Environmental Epidemiology: Basics and incorporation and application in risk assessment

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Disclaimer

The views expressed in this presentation are those of the author and do not necessarily represent the views or polices of the U.S. Environmental Protection Agency.

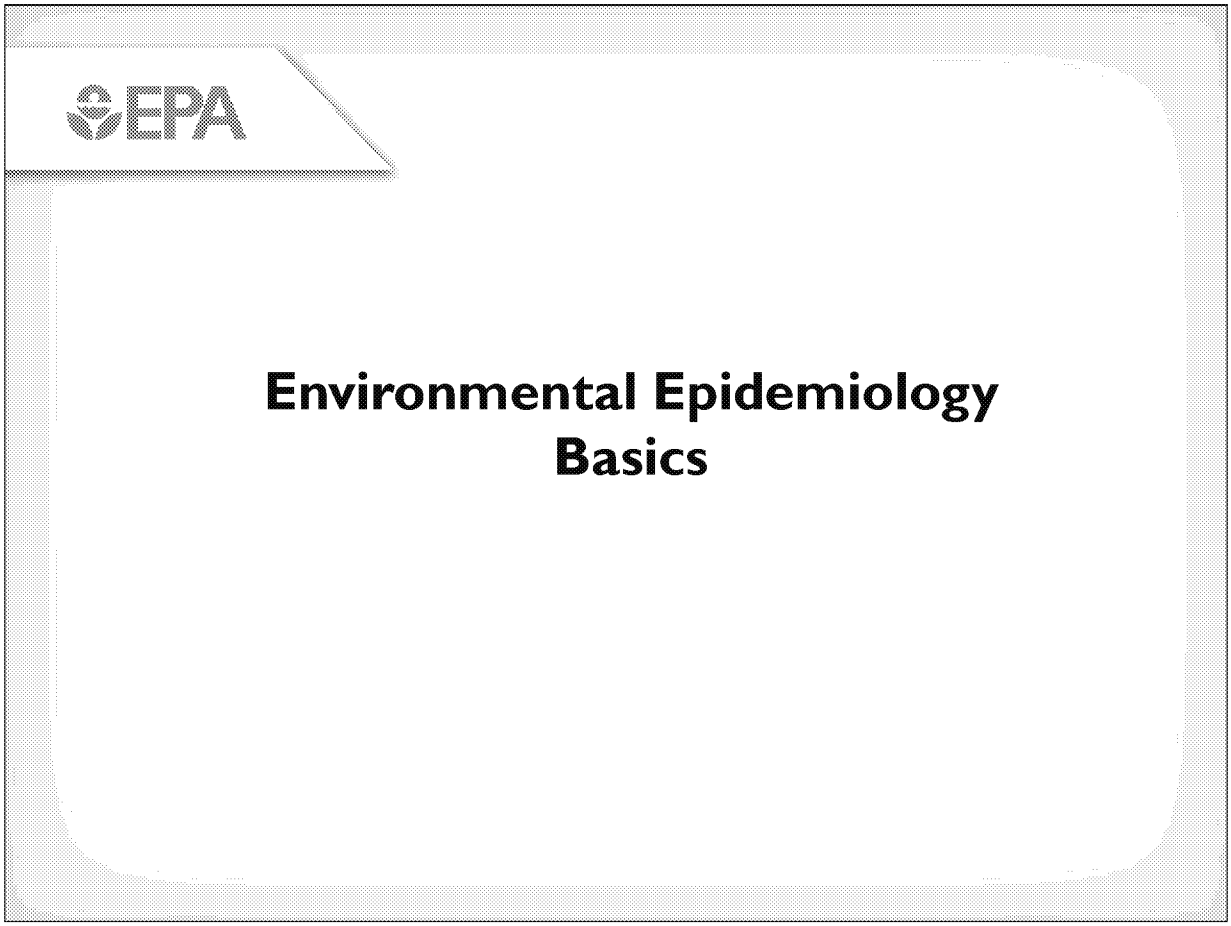
My Background

- **BS, Molecular and Cellular Biology (University of Illinois at Urbana-Champaign)**
- **MPH, Epidemiology (University of Illinois at Chicago)**
- **PhD, Environmental Epidemiology (University of Illinois at Chicago)**
  - **"Severity and Economic Burden of Recreational Waterborne Illness in the United States"**
- **Post-Doc, Epidemiologist (US EPA- Chapel Hill, NC)**
- **Epidemiologist (US EPA-RTP, NC)**

Overview

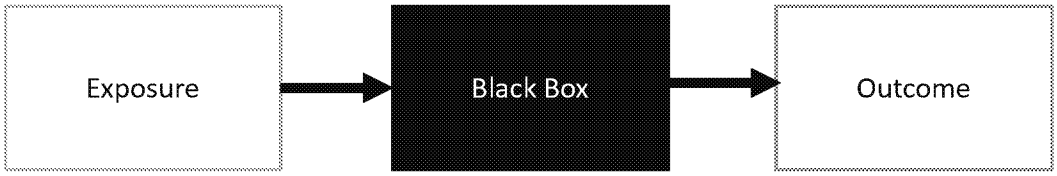
1. Environmental Epidemiology Basics

2. Environmental Epidemiology in Risk Assessment and Regulatory Decision Making
   1. Hazard Identification
   2. Exposure Assessment
   3. Dose-Response Assessment
   4. Risk Characterization


EPA
Environmental Epidemiology
Basics

What is "Epidemiology"?

- **"Epidemiology is the study of how disease is distributed in populations and the factors that influence or determine this distribution" (Gordis, 2009)**
- **Asking: Do certain exposures (or behaviors/genetics etc.) influence certain health outcomes or endpoints? Is exposure associated with the health outcome?**
- **Epidemiologic "black box"**

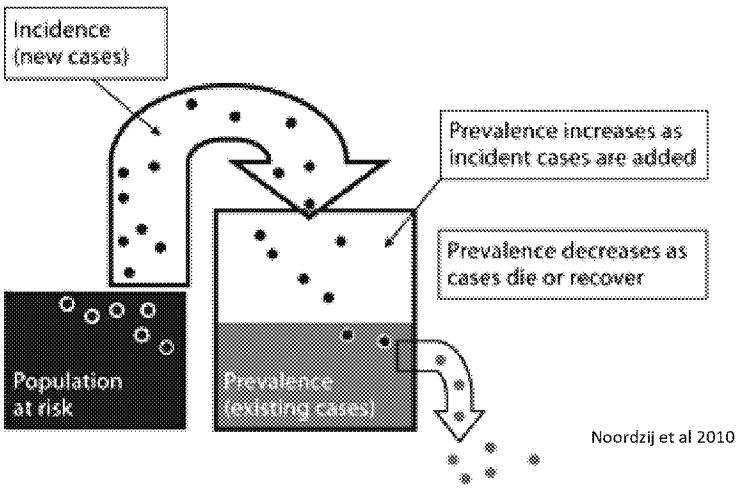


Study designs

- **Observational Study Designs (general considerations)**
  - Cross-sectional study: Basically, a survey. This type of study provides a "snapshot" of the health status of a population at a specific point in time
  - Cohort study: Study population selected based on an exposure of interest and followed in (days, months, years) to see who among them develops disease/health outcome
  - Case-control study: Study population selected according to whether they have disease/health outcome of interest. One group of people (case-subjects) have the health problem and one group does not (controls). These groups are then compared to determine the presence of specific exposures or risk factors.

Basic Epidemiology Stats

- **Incidence = # of new cases/ Population at Risk**
- **Prevalence = # of existing cases/ Population at Risk**
- **Common Epidemiology Stats Terms**
  - **Risk: # subjects developing disease /total number of subjects followed**
  - **Probability: # times something happens/ # times if COULD happen**
  - **Odds: # times something happens/ # times it DOES NOT happen**



Noordzij et al 2010

Descriptive measures and measures of association

- **Standard 2x2 Table:**

	Disease	No Disease	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	N

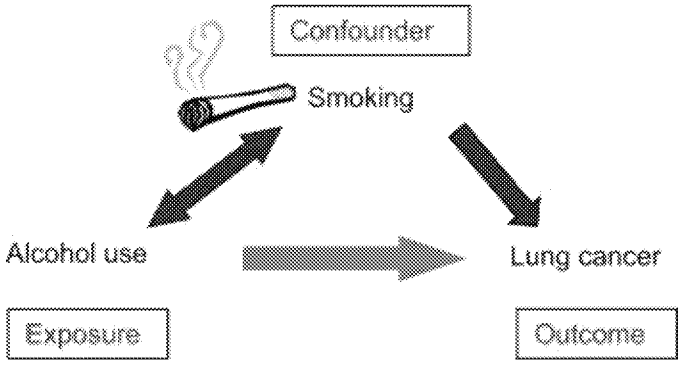
- Risk of disease among exposed= a/a+b
- Risk of disease among unexposed= c/c+d
- Relative Risk= (a/a+b)/(c/c+d)

- Odds of exposure among diseased (cases) = a/c
- Odds of exposure among those with no disease (controls) = b/d
- Odds Ratio= (a/c)/(b/d)=ad/bc

When incidence of disease >10% OR no longer approximates RR

Confounders

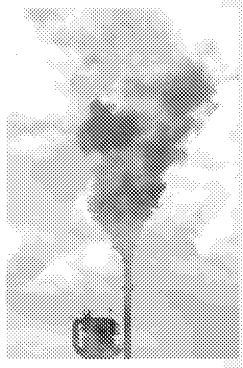
- **Associated with both exposure and health outcome**
- **Can conflate results**
- **"control" for confounders using statistical modelling**



Iles and Barrett, 2011

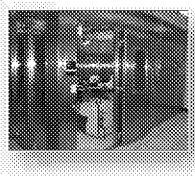
Environmental Epidemiology

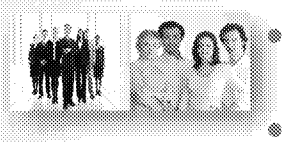
- Specifically examines exposures from the environment
  - Air pollution
    - Particulate matter, ozone
  - Water pollution
    - Chemical, microbial
  - Soil exposure
    - Lead

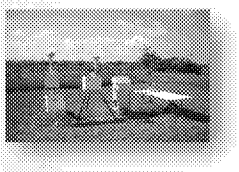


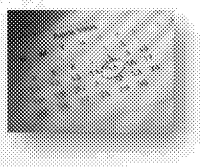
- Focused on all health outcomes
  - Subclinical symptoms (lung function)
  - Acute symptoms (Diarrhea/vomiting)
  - Chronic conditions/symptoms (asthma, COPD)
  - Mortality

Considerations







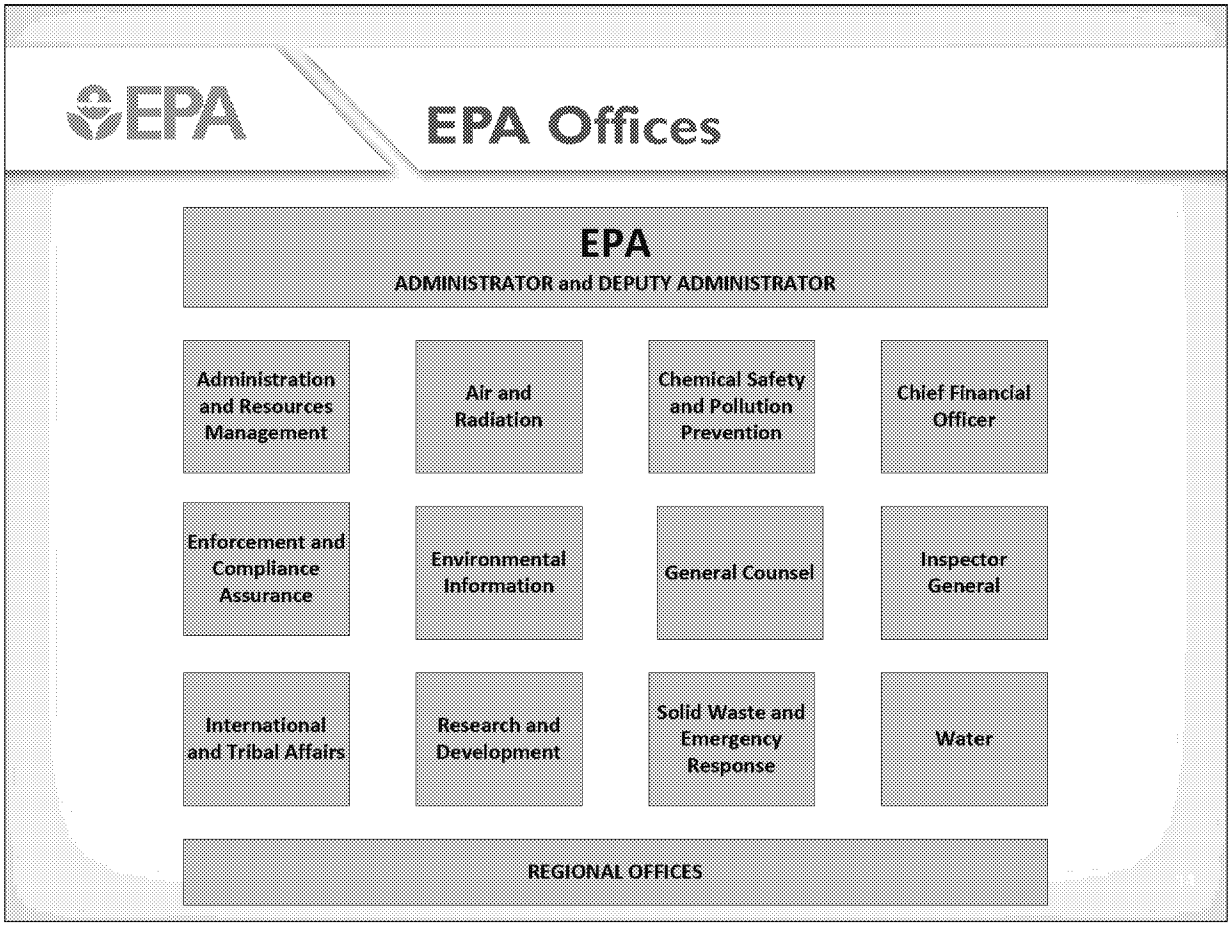


- **Chance, bias, confounding?**
- **Overall study design**
  - What kind of study design was used?
  - What is the sample size?
- **Exposure characterization**
  - What are the comparison groups?
- **Outcome**
  - How were outcomes measured?
  - How likely were non-differential and differential misclassification?
  - Was follow-up sufficient?
- **Analysis**
  - Were relevant confounders assessed properly?
  - Did exposure precede disease?

Epidemiology in Context

- In many cases epidemiology data or results can be useful for:
  - Informing risk assessment
  - Regulatory decision making
- Sometimes a single study or a small subset of studies can be used for establishing non-enforceable standards (typically)
- Other more complicated exposures or enforceable standards may require the synthesis of several types of studies including epidemiology and toxicology studies
- EPA and epidemiology
  - Mission is to protect public health and the environment
  - Conducts risk assessments

EPA Offices


EPA
ADMINISTRATOR and DEPUTY ADMINISTRATOR
Administration and Resources Management
Air and Radiation
Chemical Safety and Pollution Prevention
Chief Financial Officer
Enforcement and Compliance Assurance
Environmental Information
General Counsel
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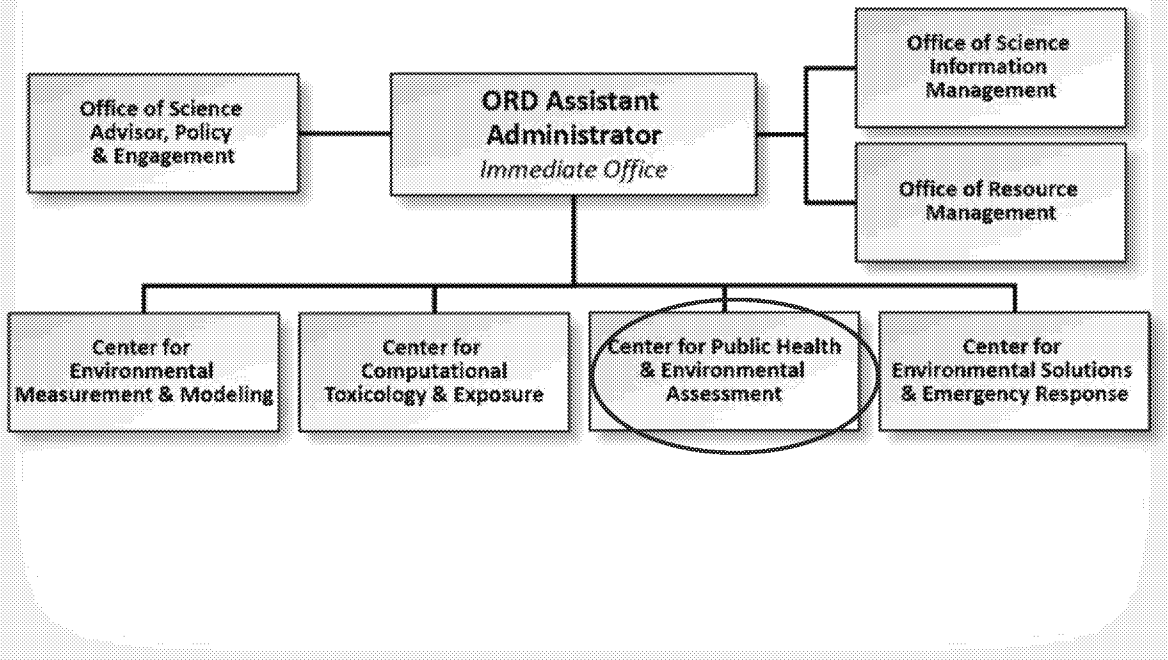
ORD Centers

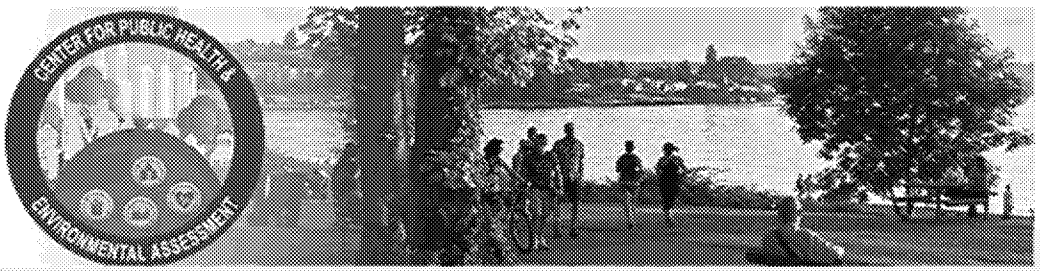

Office of Science Advisor, Policy & Engagement
ORD Assistant Administrator
Immediate Office
Office of Science Information Management
Office of Resource Management
Center for Environmental Measurement & Modeling
Center for Computational Toxicology & Exposure
Center for Public Health & Environmental Assessment
Center for Environmental Solutions & Emergency Response

Center for Public Health and Environmental Assessment

Mission: "To provide the science needed to understand the complex interrelationship between people and nature in support of assessments and policy to protect human health and ecological integrity"

CPHEA:

- **Conducts toxicological, clinical, epidemiological, ecological, and citizen science studies**
  - **To assess impact of environmental exposures/chemicals/stressors on individuals, populations, and ecosystems**
- **Develops human health and environmental assessments**
  - **To support EPA program and region policies and decisions**



EPA Risk Assessment Definition

Risk assessment:

Qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants

From EPA's "Terms of Environment" Glossary

EPA Risk Assessment

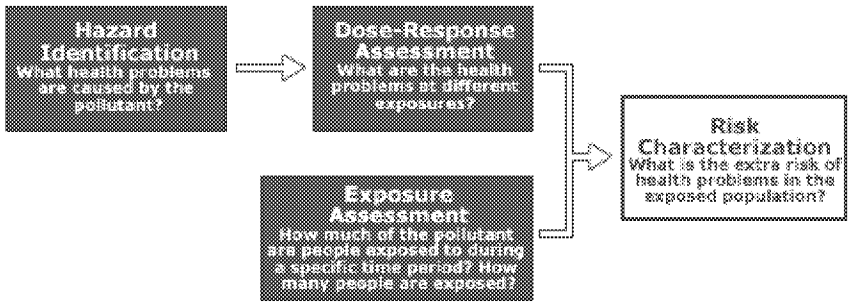
Risk assessment is the evaluation of scientific information on:

- **the hazardous properties of environmental agents,**
- **the dose-response relationship, and**
- **the extent of human exposure to those agents.**

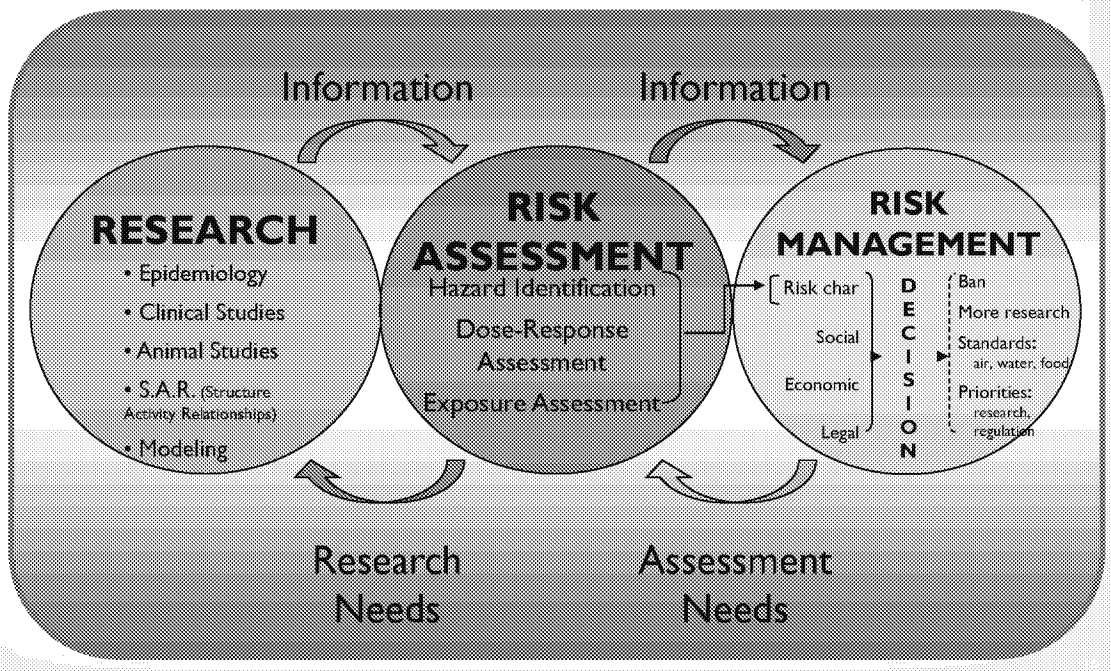
The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree.

From EPA's Glossary of IRIS Terms

The 4 Step Risk Assessment Process



Risk Analysis Paradigm



Brief History of Human Health Risk Assessment at EPA

- **1970: EPA established**
- **1975: First EPA chemical assessment (vinyl chloride)**
- **National Research Council (NRC) publications on risk assessment**
  - **1983: *Managing the Process* – the "Red Book"**
  - **1989: *Improving Risk Communication***
  - **1994: *Science and Judgment* – the "Blue Book"**
  - **1996: *Understanding Risk***
  - **2007: *Toxicity Testing in the 21st Century***
  - **2008: *Phthalates and Cumulative Risk Assessment***
  - **2009: *Science and Decisions* – the "Silver Book"**

Evidence from Epidemiologic Studies

Results from epidemiologic studies can be used in two ways to support risk assessment and regulatory decision making:

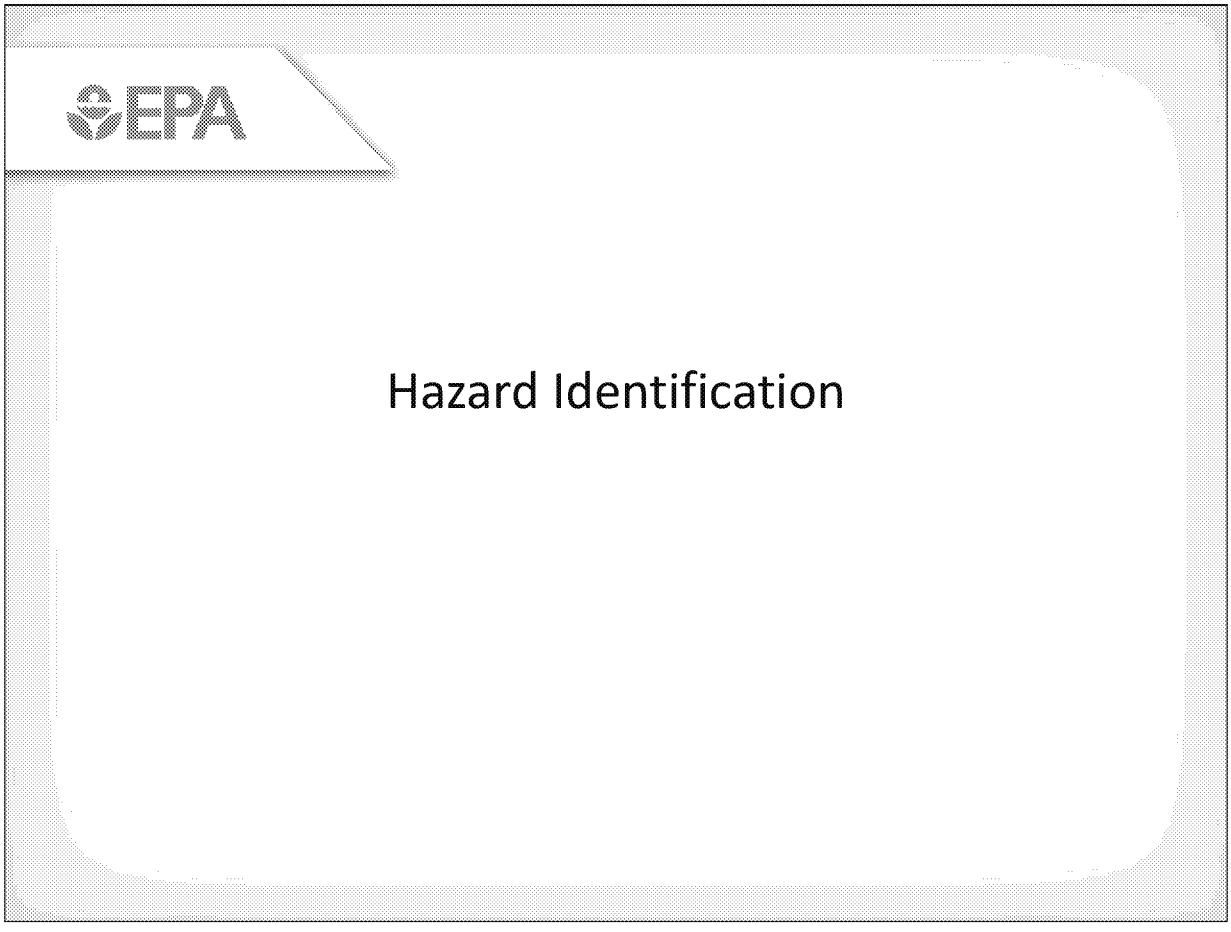
1. **Qualitatively,** to inform the hazard identification aspect of risk assessment; and

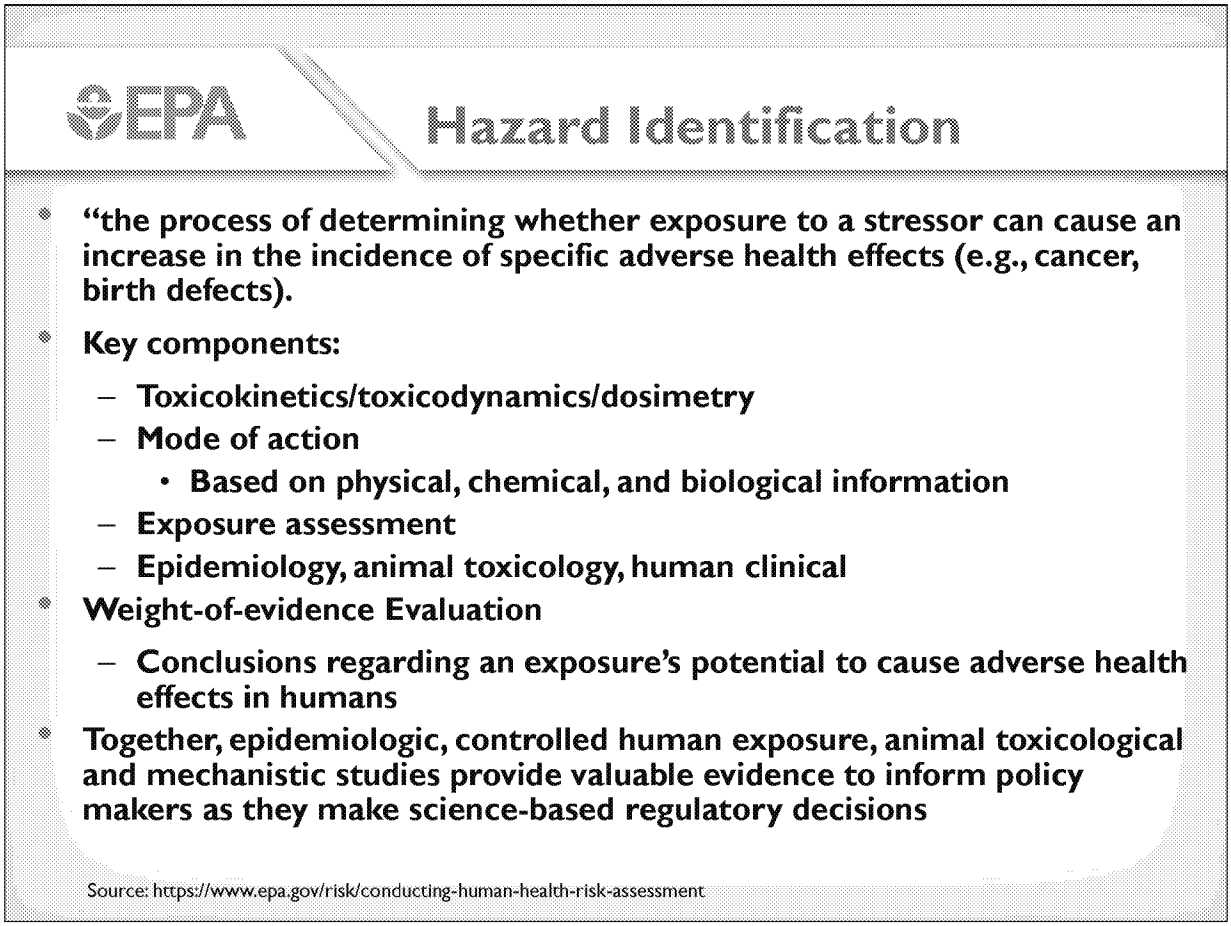
2. **Quantitatively,** to inform hazard identification, exposure assessment, dose-response relationship and/or the health impact (burden) component of risk assessment

Epidemiology "asks"

Risk Assessment Step	Priority Asks for Risk Assessment		
Hazard ID	Confirm outcome	Confirm exposure	Report methods fully and transparently
Dose Response	Include information on shape of curve	Evaluate concordance with previous results	Describe direction/magnitude of error
Exposure Assessment	Describe source-to-intake pathways	Describe complete exposure data	Describe direction/magnitude of error

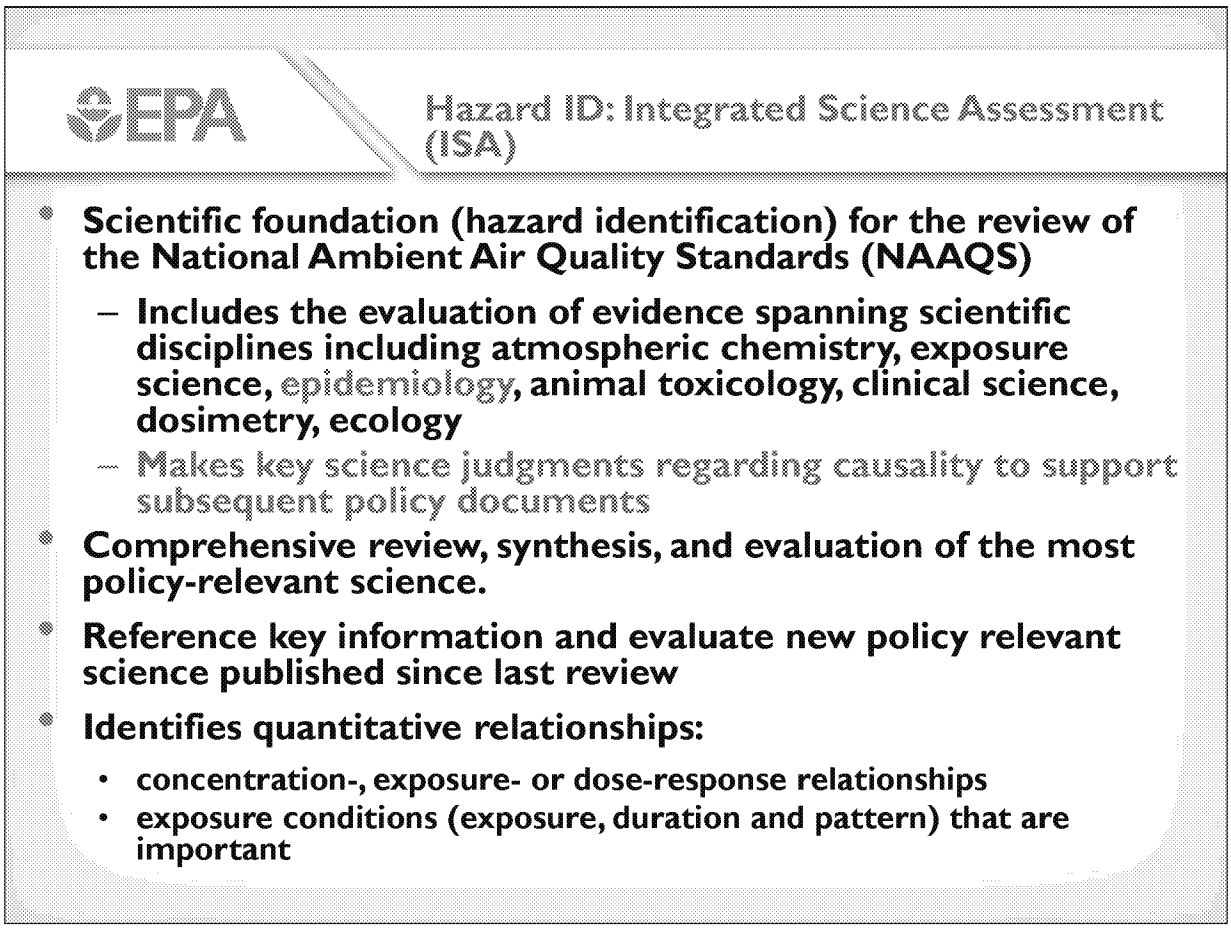
CJ Burns et al 2019


EPA
Hazard Identification

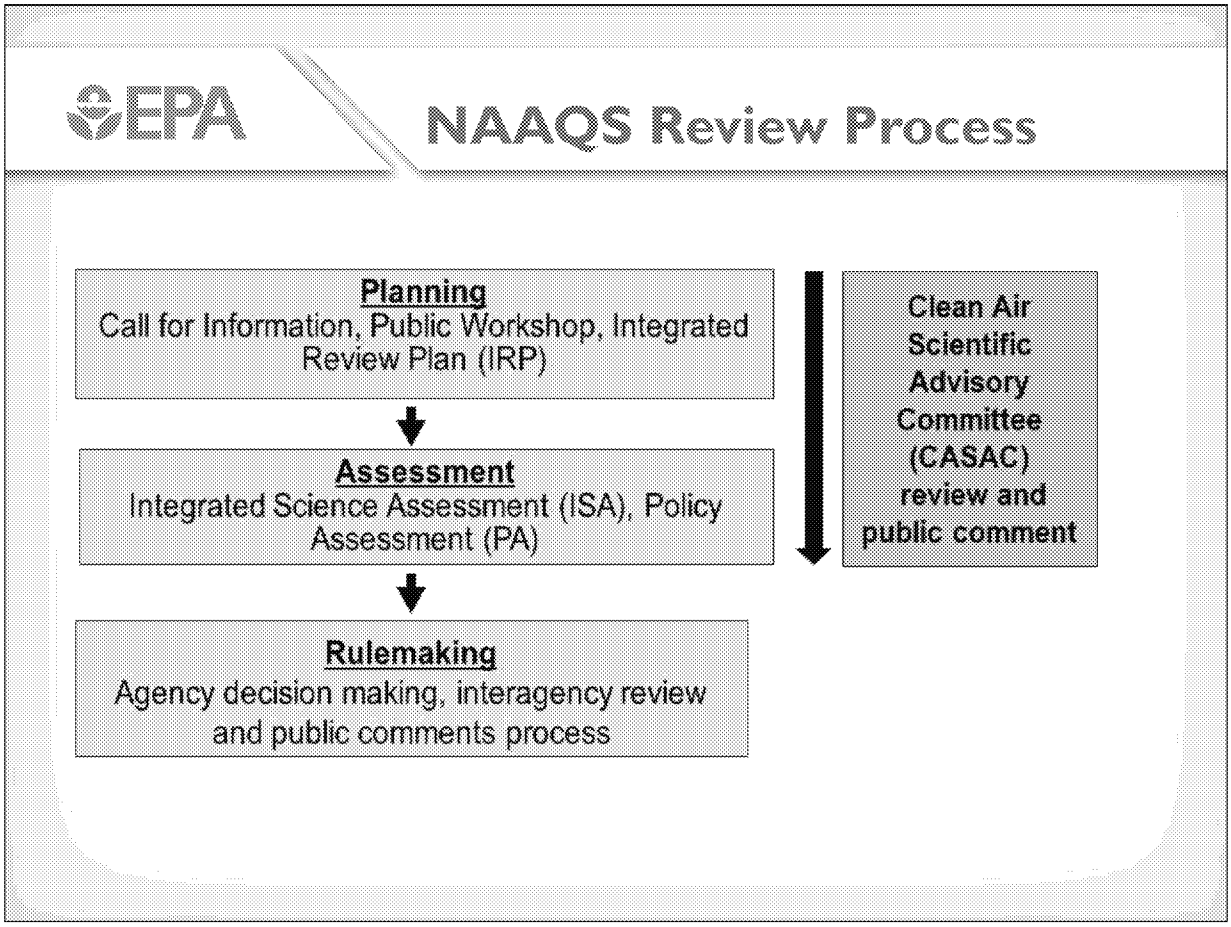


The evaluation of health evidence that can be used to inform regulatory policy can come from epidemiologic, animal toxicological and controlled human exposure studies. In an ideal scenario, you would have substantial evidence bases from all three scientific disciplines. Experimental studies (these are the animal toxicological studies and the controlled human exposure studies) are useful in distinguishing the independent effect of a chemical or pollutant from an effect that could be due to a co-occurring pollutant or chemical or other potential confounding factors.

On the other hand, observational epidemiologic studies provide information on effects occurring at real-world or ambient concentrations, and may include a range of individuals with different ages and health status who might be at greatest risk. Epidemiologic studies are also able to evaluate certain health outcomes, ED visits for example, that can't be measured in experimental studies.



More on ISAs and the regulatory process from Jason Sacks at EPA next week



Clean Air Act: Requires periodic (every 5 years) review of science in which NAAQS are based on
Six criteria pollutants: Particulate matter, ozone, lead, CO, NO2, SO2
Very ambitious time-line

NAAQS Table

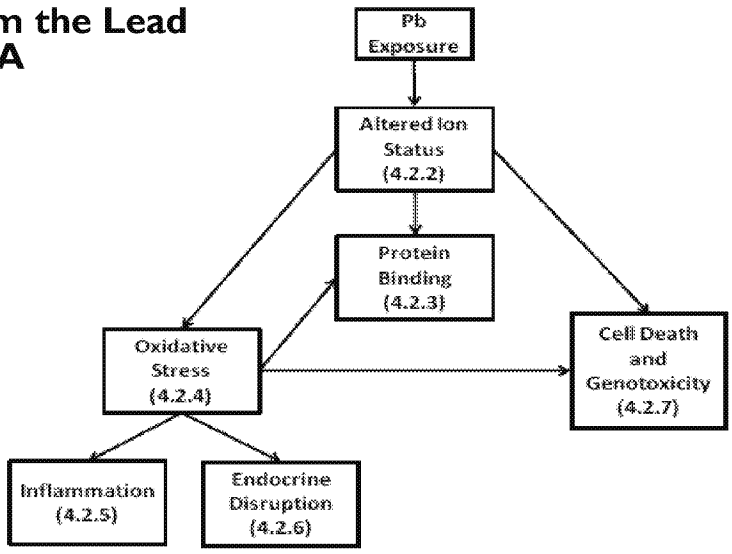
Pollutant [links to historical tables of NAAQS reviews]		Primary/ Secondary	Averaging Time	Level	Form
Carbon Monoxide (CO)		primary	8 hours	9 ppm	Not to be exceeded more than once per year
			1 hour	35 ppm	
Lead (Pb)		primary and secondary	Rolling 3 month average	0.15 µg/m^3 (1)	Not to be exceeded
Nitrogen Dioxide (NO_2)		primary	1 hour	100 ppb	98th percentile of 1-hour daily maximum concentrations, averaged over 3 years
		primary and secondary	1 year	53 ppb (2)	Annual Mean
Ozone (O_3)		primary and secondary	8 hours	0.070 ppm (3)	Annual fourth-highest daily maximum 8-hour concentration, averaged over 3 years
Particle Pollution (PM)	$PM_{2.5}$	primary	1 year	12.0 µg/m^3	annual mean, averaged over 3 years
		secondary	1 year	15.0 µg/m^3	annual mean, averaged over 3 years
		primary and secondary	24 hours	35 µg/m^3	98th percentile, averaged over 3 years
	PM_{10}	primary and secondary	24 hours	150 µg/m^3	Not to be exceeded more than once per year on average over 3 years
Sulfur Dioxide (SO_2)		primary	1 hour	75 ppb (4)	99th percentile of 1-hour daily maximum concentrations, averaged over 3 years
		secondary	3 hours	0.5 ppm	Not to be exceeded more than once per year

Recently completed

https://www.epa.gov/criteria-air-pollutants/naaqs-table

Mode of Action

Example from the Lead (Pb), 2013 ISA



Note: The subsections where these MOAs are discussed are indicated in parentheses.
(Section 4.2.2; Section 4.2.3; Section 4.2.4; Section 4.2.5; Section 4.2.6; and Section 4.2.7).

Figure ES-2 Schematic representation of the relationships between the various MOAs by which Pb exerts its effects.

Weight of Evidence Approach

- How does the collection of studies address chance, bias, and confounding as explanations for the observed association between an exposure and a disease?
- Weight can be given to studies with greater validity and/or precision, but this may not be straightforward.
  - Precision and validity may be inversely related
- Tools
  - Chance
    - Evaluate the patterns of associations across studies
  - Bias
    - Examine effect of study attributes
      - For example, consider type of exposure assessment. Are stronger effects seen with methods that have less non-differential misclassification?
  - Confounding
    - Could be evaluated and controlled for differently across studies

Integrated Science Assessments (ISAs)

Weight-of-Evidence for Causal Determination

Source: Preamble to Integrated Science Assessments (https://www.epa.gov/isa)

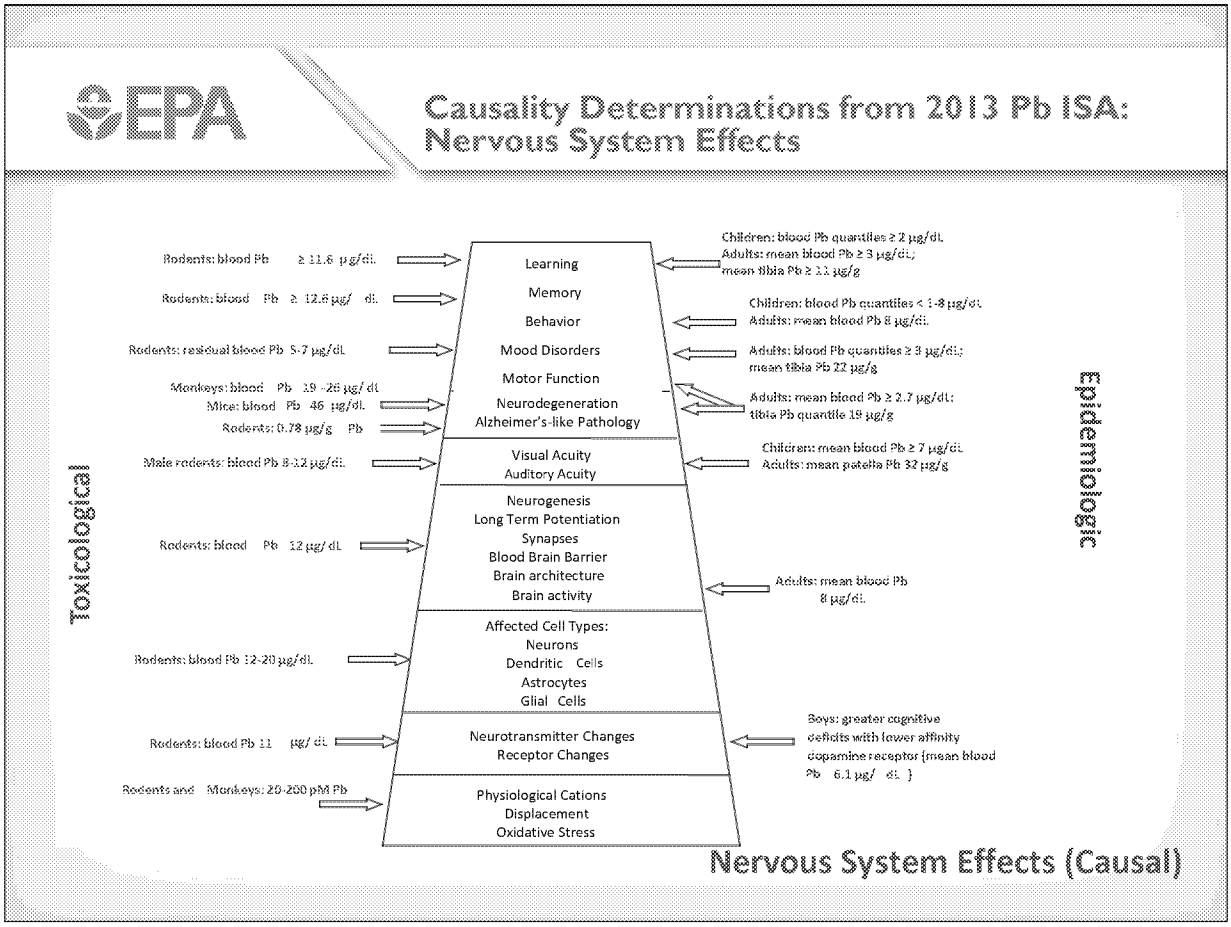
Table II Weight of evidence for causal determination.

	Health Effects	
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g., doses or exposures generally within one or two orders of magnitude of recent concentrations [...] pollutant has been shown to result in [...] effects in studies in which chance, confounding, other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent [...] effects; or (2) observational studies that can be explained by plausible alternatives or that are supported by other lines of evidence (e.g., [...] studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.	[...] evidence that is consistent directly to infer a causal relationship is usually obtained from the joint
Likely to be a causal relationship	Evidence is sufficient to conclude that there is a relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases, but uncertainties remain in the overall. For example: (1) observational studies show an association, but [...] pollutant exposures are difficult to address, and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.	[...] example, field studies show a relationship, but suspected interacting factors cannot be controlled, and other lines of evidence are limited or inconsistent. Generally, the determination is based on multiple studies by multiple research groups.
Suggestive, but not sufficient, to infer a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited, and chance, confounding and other biases cannot be ruled out. For example, (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species; or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g., animal studies or mode of action information) to support the determination.	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but chance, confounding, and other biases cannot be ruled out. For example, at least one high-quality study shows an effect, but the results of other studies are inconsistent.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and lifestages, are mutually consistent in not showing an effect at any level of exposure.	Several adequate studies, examining relationships with relevant exposures, are consistent in failing to show an effect at any level of exposure.

… doses or exposures generally w/in 1-2 orders of magnitude of recent concentrations

. . . chance, confounding, and other biases could be ruled out with reasonable confidence

. . . multiple high-quality studies by multiple research groups

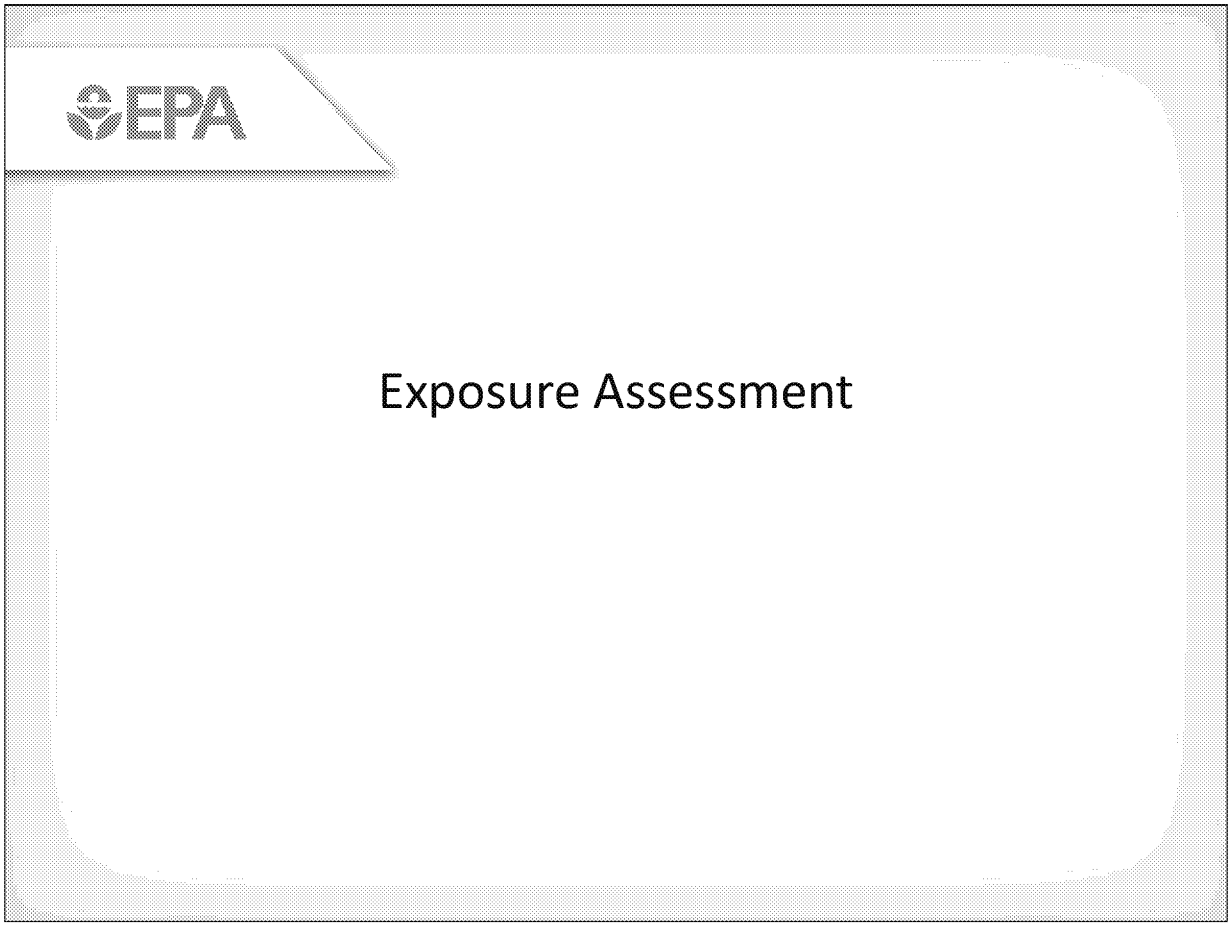


First, I wanted to show this figure that demonstrates how epidemiologic and toxicological evidence are integrated qualitatively to reach a causal determination. This is an example for how Pb causes nervous system effects. I'll note that this figure was not included in the Pb ISA, but developed internally to help us synthesize and integrate the evidence. The pyramid in the middle includes different neurological endpoints, with the least severe along the bottom and the most severe at the top. The idea is to show where there is evidence for the progression of these different neurological endpoints due to Pb exposure. The evidence from animal toxicological studies is in green on the left side of the pyramid and the epidemiologic evidence is in purple on the right side of the pyramid.

Summary of Causality Determinations from 2013 Pb ISA

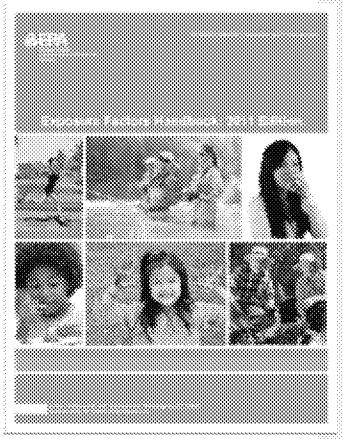
Table 1-4 Summary of causal determinations for health and ecological effects.

Outcome/Effect	Human Health Causal Determination[a]	Ecological Receptors Causal Determination[a]
Nervous System Effects[b]	Causal Relationship: Cognition, Attention, Impulsivity and Hyperactivity in Children	Likely Causal Relationship: Neurobehavioral Effects in Terrestrial and Freshwater Invertebrates and Vertebrates
Cardiovascular Effects	Causal Relationship: Hypertension and Coronary Heart Disease	N/A[c]
Renal Effects	Likely Causal Relationship: Reduced Kidney Function	N/A[c]
Immune Effects	Likely Causal Relationship: Atopic and Inflammatory Conditions, Decreased Host Resistance	N/A[c]
Hematological Effects[c]	Causal Relationship: RBC Function and Survival, Altered Heme Synthesis	Causal Relationship: ALAD Activity in Terrestrial and Freshwater Vertebrates Likely Causal Relationship: ALAD activity in Freshwater Invertebrates
Reproductive and Developmental Effects[d]	Causal Relationship: Developmental and Male Reproductive Function	Causal Relationship: Invertebrates and Vertebrates
Cancer	Likely to be a causal relationship	N/A[c]


EPA
Exposure Assessment

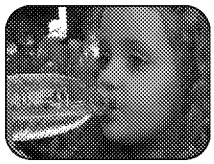
Exposure Assessment

- **Identifying the pathways by which toxicants may reach individuals, estimating how much of a chemical an individual is likely to be exposed to, and estimating the number likely to be exposed (EPA's Terms of Environment).**
- **The determination or estimation (qualitative or quantitative) of the magnitude, frequency, or duration, and route of exposure (EPA's Exposure Factors Handbook).**

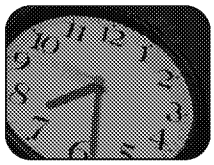


Exposure Specifications

- **Exposure Medium and Route**
  - **Inhalation– air**
  - **Oral– water, soil, food**
  - **Dermal– soil, water, food, air**



- **Exposure Duration**
  - **Acute**
  - **Short-term**
  - **Longer-term**
  - **Chronic**



- **Potentially Exposed Populations**
  - **Workers**
  - **Emergency Responders or victims**
  - **Pregnant women**
  - **Children or the elderly**

Example: Quantitatively estimating exposure to beach water

Journal of Exposure Science and Environmental Epidemiology (2017) 00, 1–8

www.nature.com/jes

ORIGINAL ARTICLE

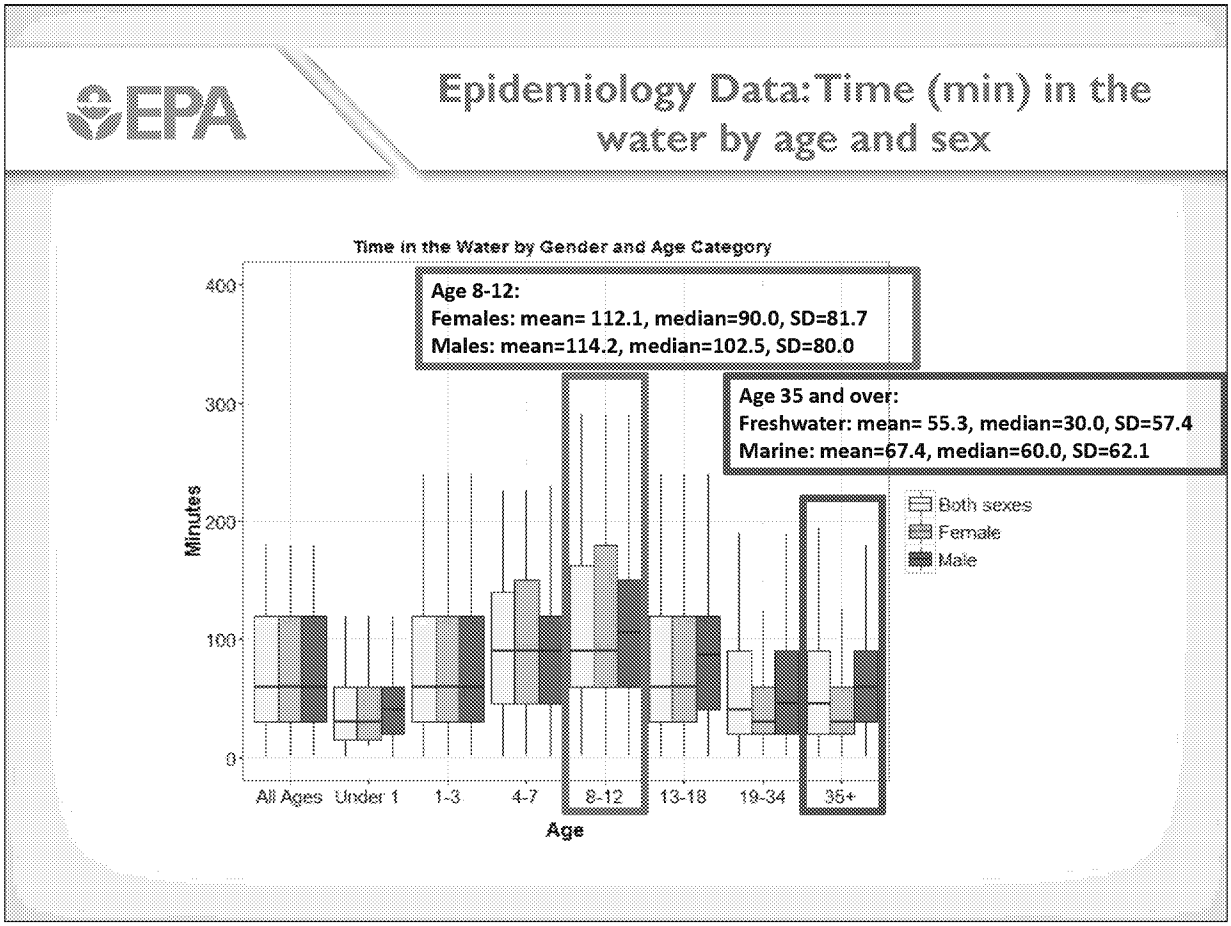
Child environmental exposures to water and sand at the beach: Findings from studies of over 68,000 subjects at 12 beaches

Stephanie DeFlorio-Barker[1], Benjamin F. Arnold[2], Elizabeth A. Sams[1], Alfred P. Dufour[3], John M. Colford Jr[2], Steven B. Weisberg[4], Kenneth C. Schiff[5] and Timothy J. Wade[1]

Swimming and recreating in lakes, oceans, and rivers is common, yet the literature suggests children may be at greater risk of illness following such exposures. These effects might be due to differences in immunity or differing behavioral factors such as poorer hygiene, longer exposures to, and greater ingestion of potentially contaminated water and sand. We pooled data from 12 prospective cohorts ($n = 68,685$) to examine exposures to potentially contaminated media such as beach water and sand among children compared with adults, and conducted a simulation using self-reported time spent in the water and volume of water swallowed per minute by age to estimate the total volume of water swallowed per swimming event by age category. Children aged 4–7 and 8–12 years had the highest exposures to water, sand, and algae compared with other age groups. Based on our simulation, we found that children (6–12 years) swallow a median of 36 ml (90th percentile = 150 ml), whereas adults aged ≥ 35 years swallow

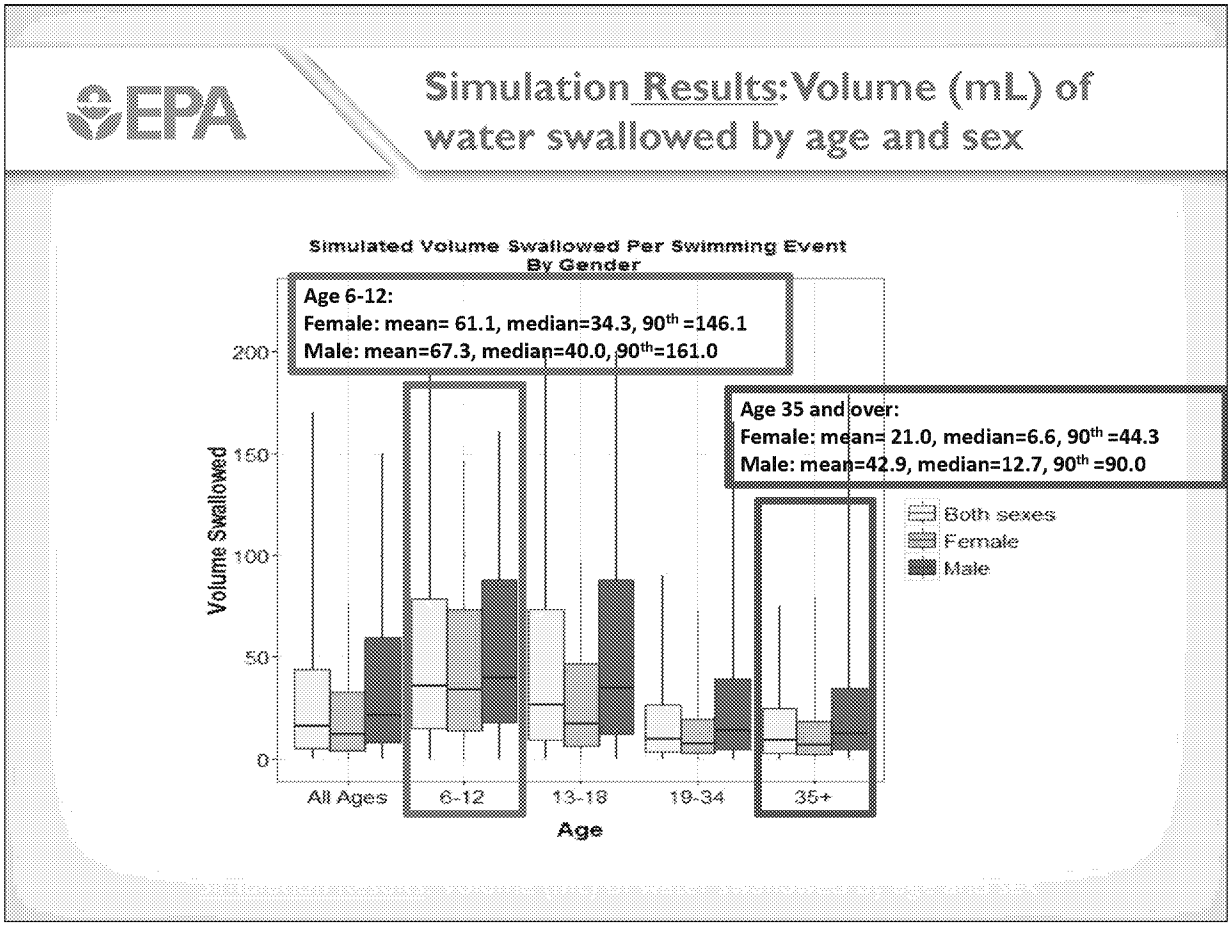
Used data from NEEAR studies (and other studies conducted in California) to estimate the time spent in the water and the amount of water swallowed during water recreation
Integrating 2 unique sources of data:
Pooled epidemiology data on ~68,000 participants at 12 beaches in the US
Recently published in American Journal of Public Health (Arnold et al 2016)
Rate of water ingested while swimming in swimming pool
Recently published in Journal of Water and Health (Dufour et al 2017)

Using epidemiology data: Tabulate the frequency of certain behaviors at the beach among different age groups
Using both epidemiology and ingestion rate data: Estimate volume of water swallowed by age group and sex per event

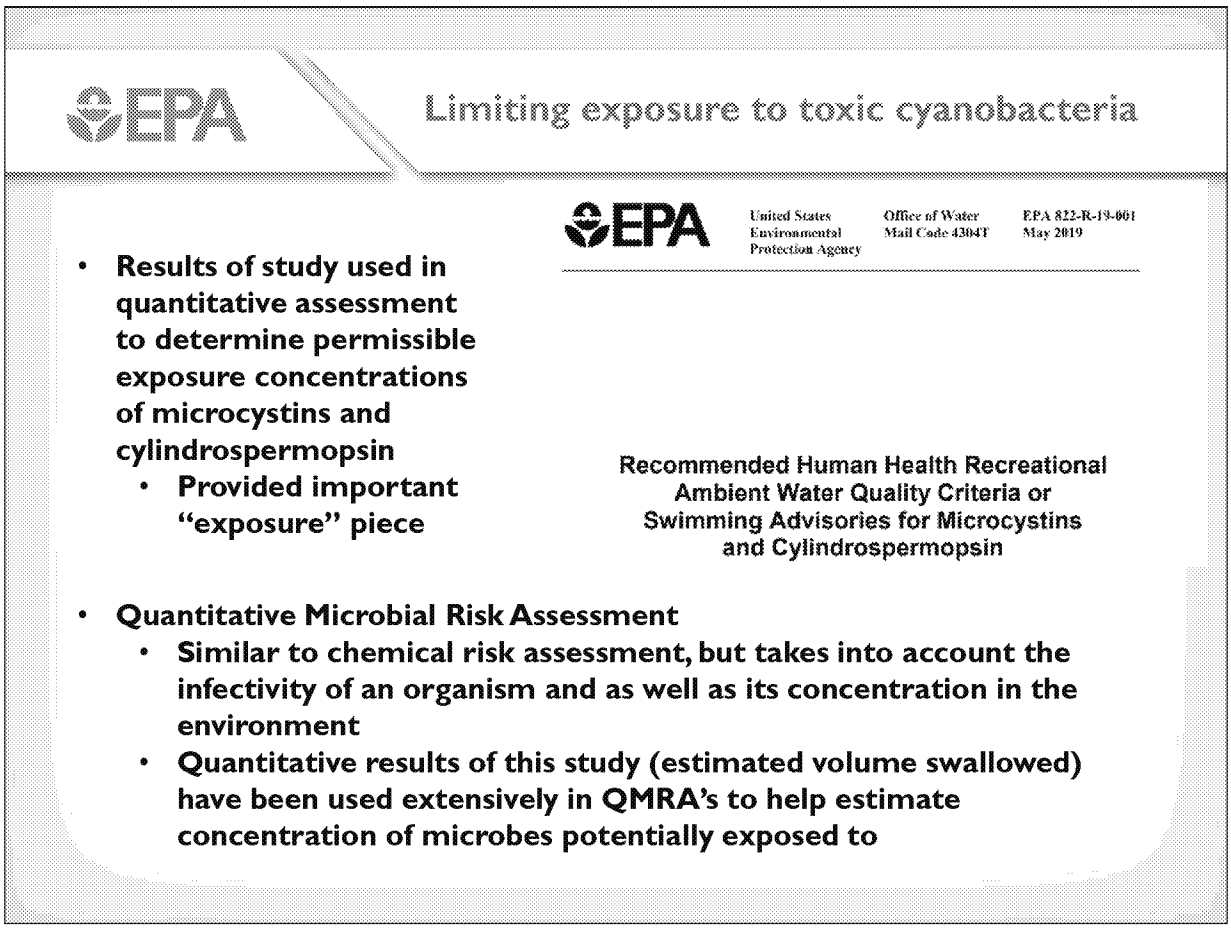


Using data from the epi studies:

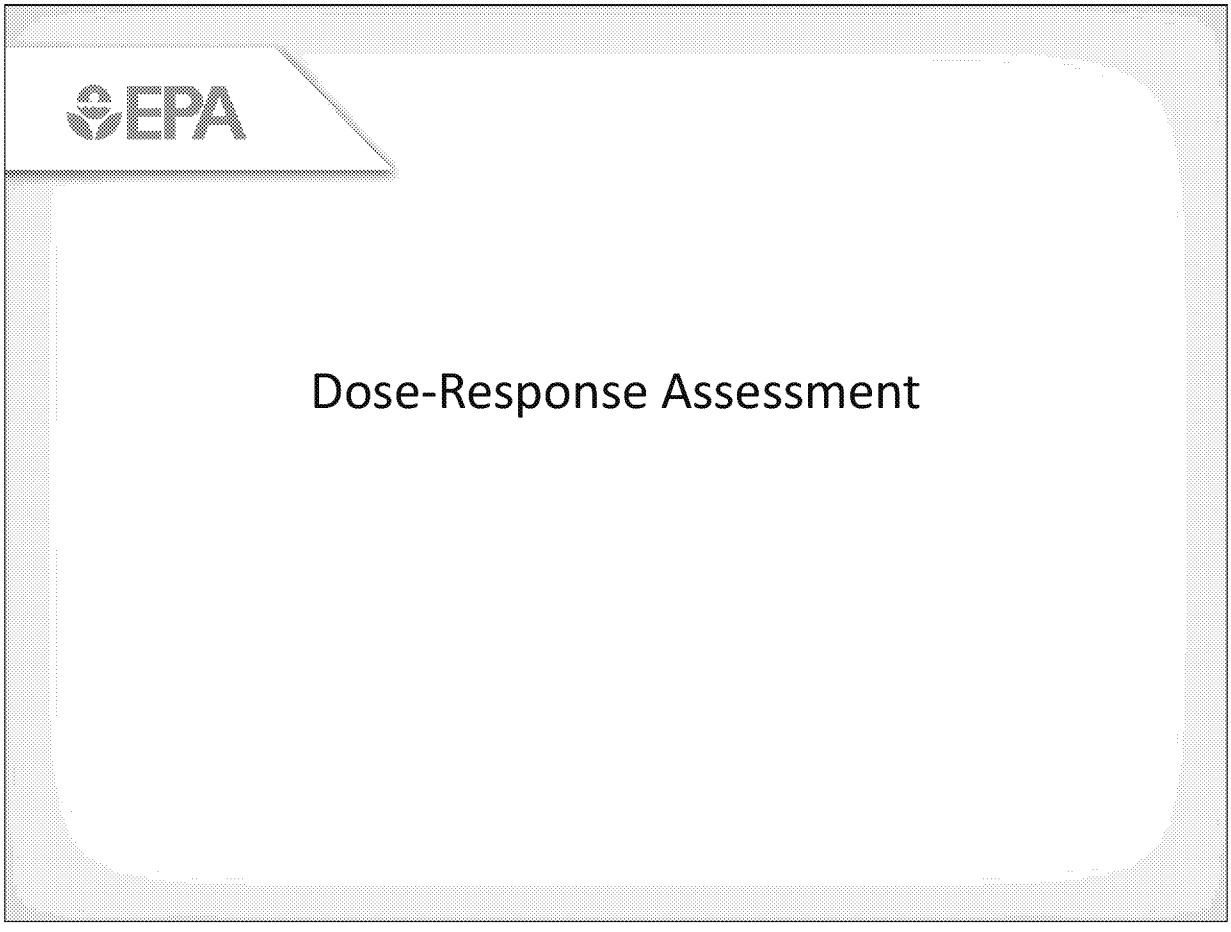
Males generally spent more time in water compared to females



Children swallow more water per swimming event compared to adults
Males swallow more water than females
Males tend to spend more time in water, and swallow more water per minute (Dufour et al 2017)

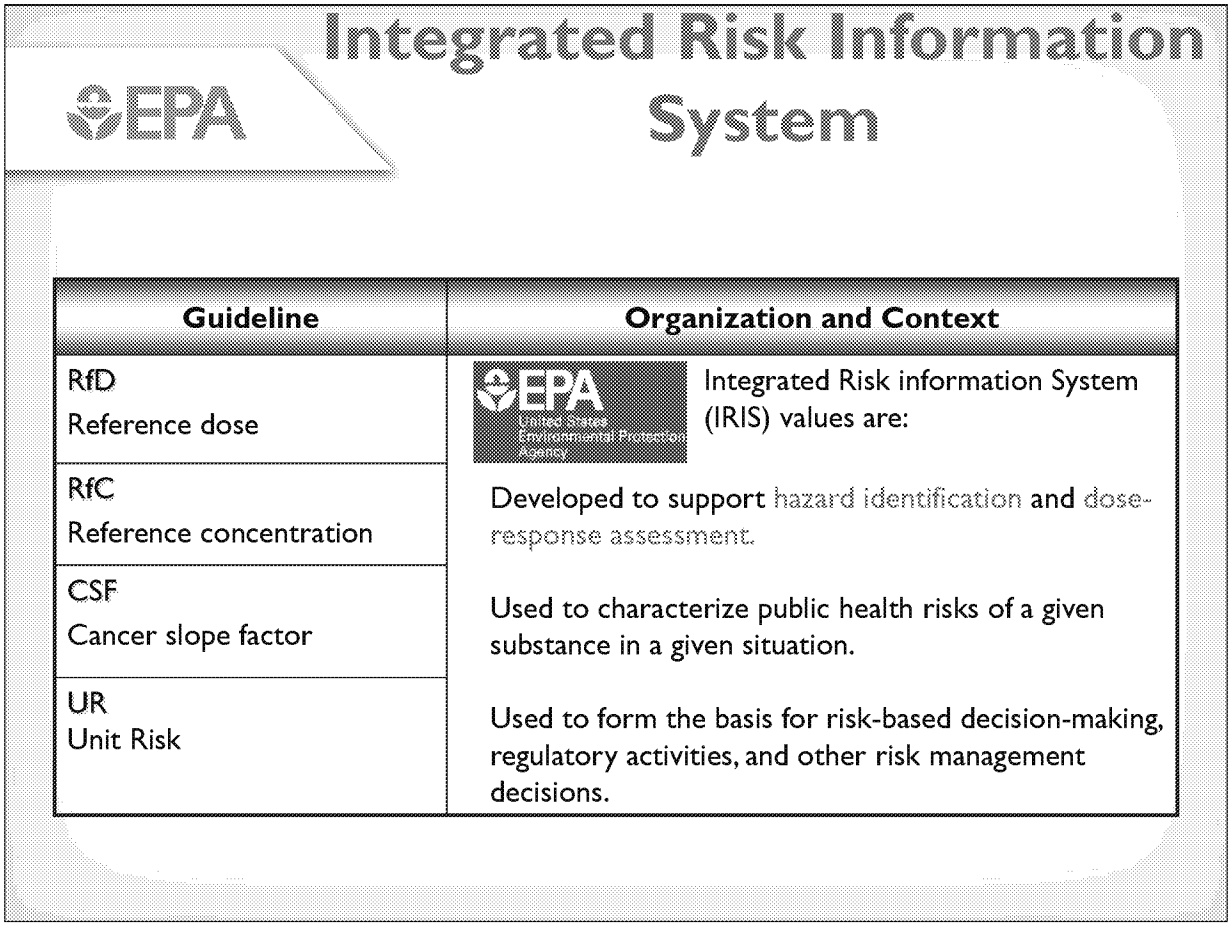


Results used to help set recommended criteria for microsystins and clylindosperompsin (produced by a variety of toxigenic cyanobacteria – AKA- blue-green algae)


EPA
Dose-Response Assessment

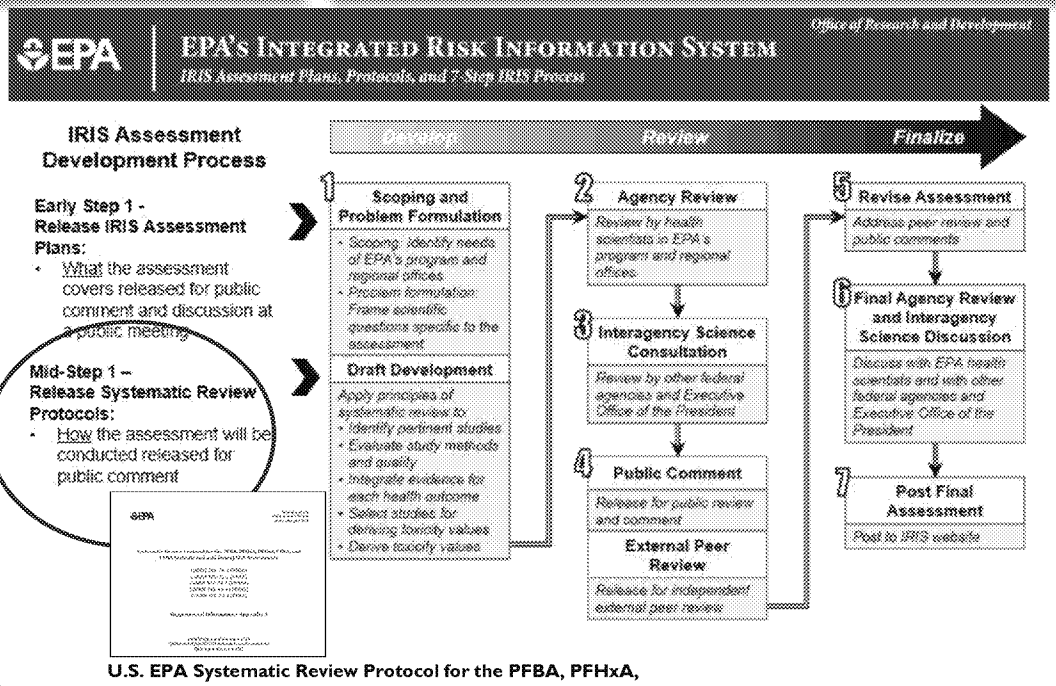
Dose-Response Assessment

- **Evaluating the quantitative relationship between dose and toxicological responses.** (EPA's Terms of the Environment)
- **A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response.**
- **Response can be expressed as:**
  - **Measured or observed incidence or change in level of response**
  - **Percent response in groups of subjects (or populations)**
  - **Probability of occurrence or change in level of response within a population.** (EPA's IRIS Glossary)



IRIS includes EPA-derived guidelines for inhalation and oral routes of exposure.
IRIS values can be used in combination with exposure information to characterize the public health risks of a given substance in a given situation
Risk characterizations can then form the basis for risk-based decision-making, regulatory activities, and other risk management decisions designed to characterize and protect public health.
There are two general types of human health reference values in IRIS – noncancer and cancer.
For noncancer effects (or effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action)
RfDs - Reference doses for oral exposure (ingestion)
RfCs – Reference concentrations for inhalation exposure
For cancer effects:
Cancer slope factors, sometimes called oral slope factors.
Oral and inhalation unit risks for carcinogenic effects.
For carcinogens, there also are descriptors that characterize the weight of evidence for human carcinogenicity in IRIS. Weight-of-evidence is a system used by the EPA for characterizing the extent to which the available data support the hypothesis that an agent causes cancer in humans.

Progress



U.S. EPA Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments released January 2021

Example: IRIS Assessments

- **IRIS: Integrated Risk Information System**
  - **Online database provides qualitative and quantitative to help with decision making**
  - **Hazard identification and dose-response assessment components**
- **As of June 2007, 44 of the 545 chemical assessments were identified as using human data to develop toxicity values (RfC, RfD, IUR, CSF)** (Persad and Cooper, 2007)
  - **Other assessments mostly relied on animal data**

Benzene IRIS Assessment

Used human health (epidemiology) data to develop all toxicity values (example below)

Median exposure (ppm; 8-hr TWA)	Number of subjects	ALC (mean ± SD × 10^2/μL blood)	Transformed exposures
0.02 (control)	44	1.9 ± 0.4	0.0198
13.6	22	1.6 ± 0.3	2.68
91.9	22	1.3 ± 0.3	4.53

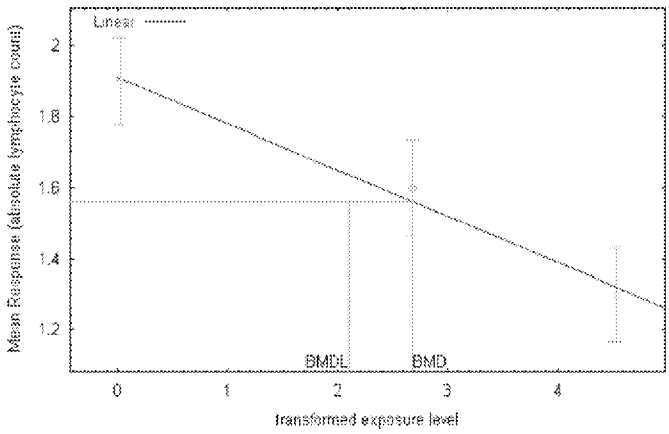
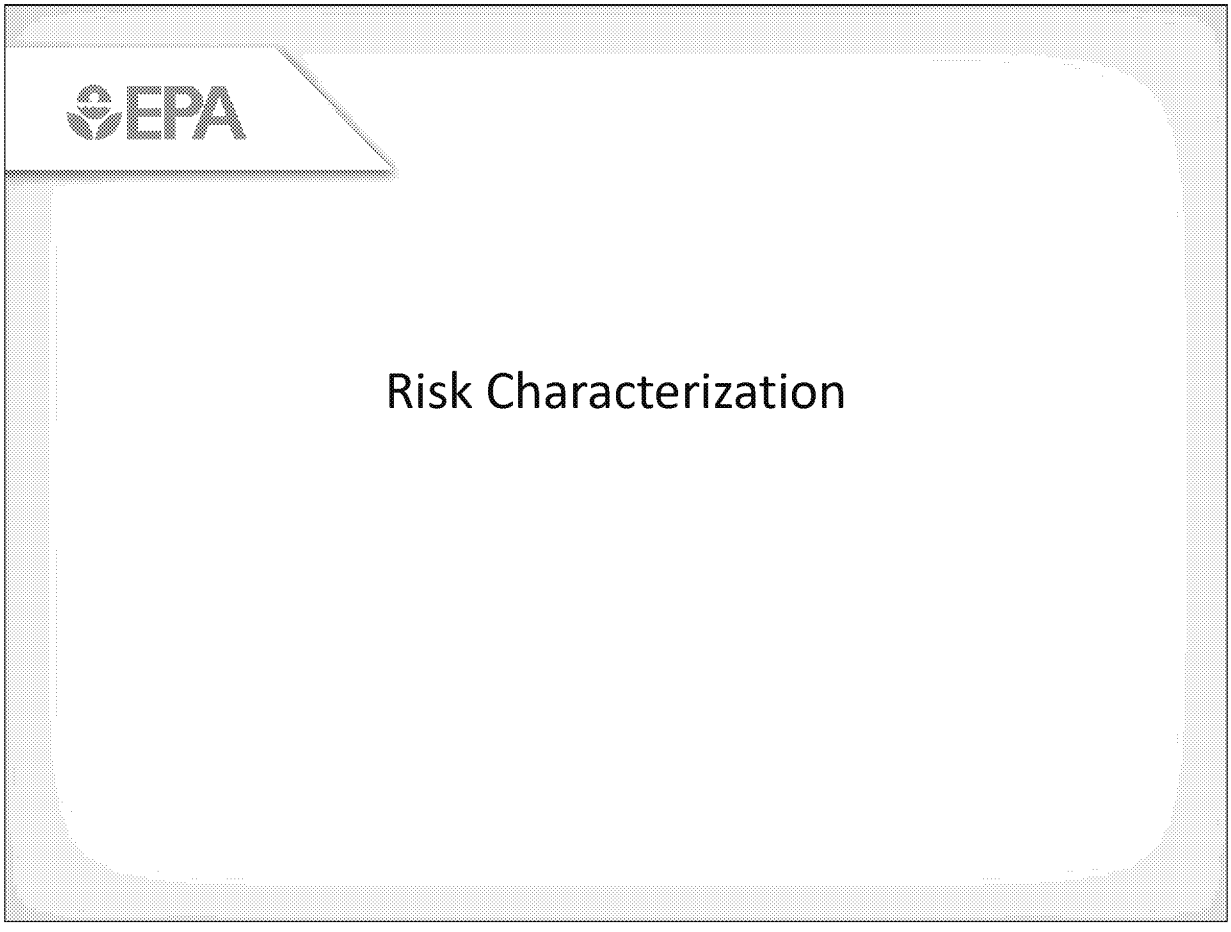


Figure 2. Linear model of ALC data from Rothman et al. (1996a).

- **Developed by Rothman et al**
  - **Epidemiologic occupational inhalation study.**
  - **Chinese factory workers**
  - **Used to develop both RfC and RfD**

BMD: Benchmark Dose
BMDL: 95% lower confidence limit of BMD

Source: Toxicological review of Benzene (Noncancer effects)


EPA
Risk Characterization

Risk Characterization

- **The last phase of the risk assessment process that estimates the potential for adverse health or ecological effects to occur from exposure to a stressor and evaluates the uncertainty involved.**

(EPA's Terms of Environment)

- **The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.**

(EPA's IRIS Glossary)

EPA

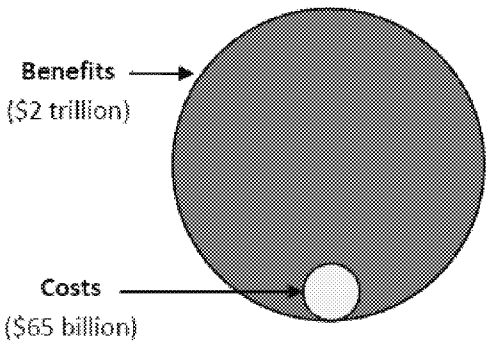
Using Epidemiology in Benefits Analysis

BenMAP COMMUNITY EDITION

Why Estimate the Benefits of an Air Quality Policy?

- **Answers the basic question:**
  - **What are the health and economic benefits of emissions controls and the associated improvements in air quality?**
- **To compare benefits against the costs of a policy**
- **Can help decide between different policies**
- **Can improve efficiency and effectiveness**
- **Can help determine if a particular policy is "worth it" to society**

Benefits and Costs of the U.S. Clean Air Act

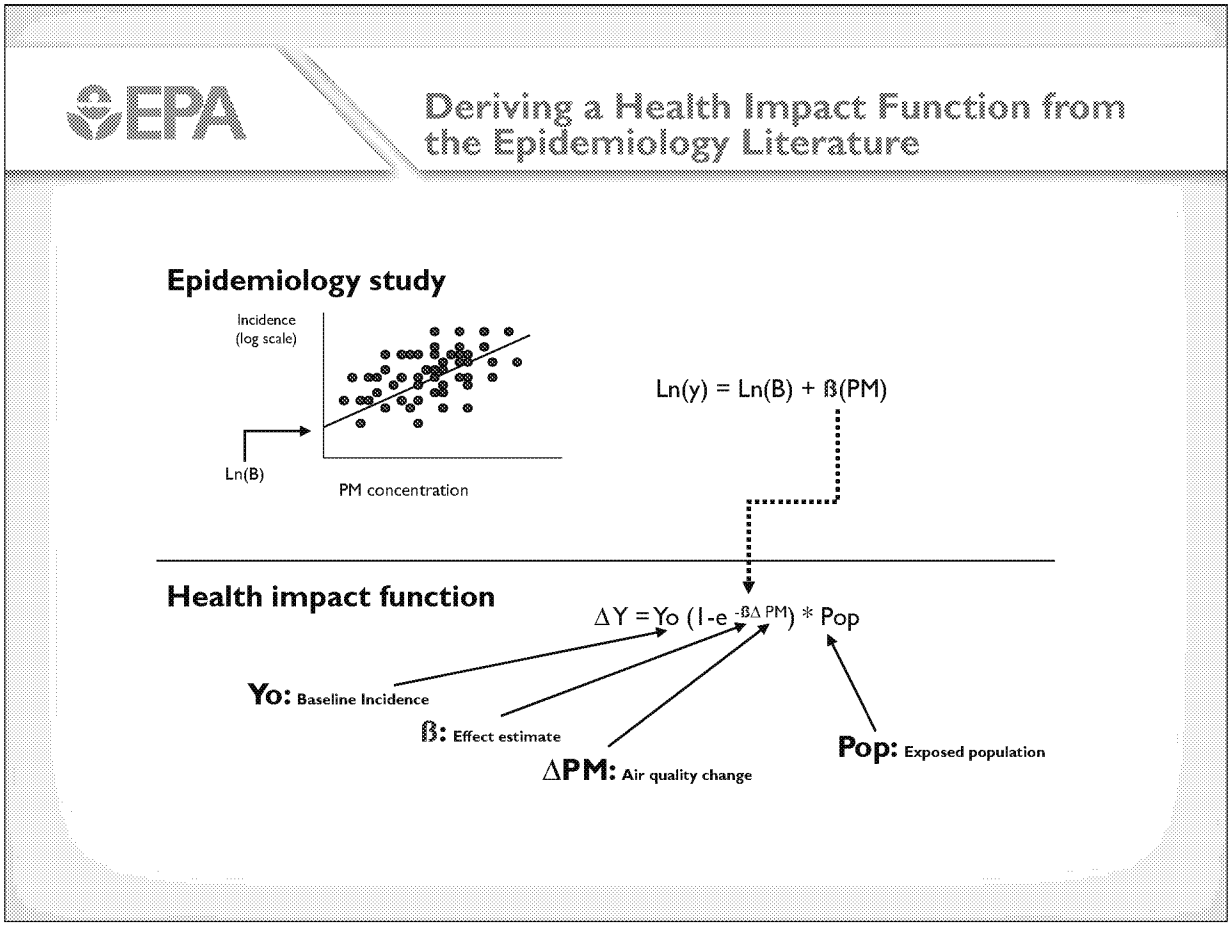


Source: Section 812 Analysis of the Benefits and Costs of the Clean Air Act

Section 812 Analysis of the Benefits and Costs of the Clean Air Act
Costs are incurred by industries that are targeted for reductions in emissions of the NAAQS pollutants.
The actual setting of the standard does not allow for the consideration of costs. Costs are only considered in developing control strategies during the implementation process.

How does EPA estimate the health and economic impacts associated with changes in air quality?

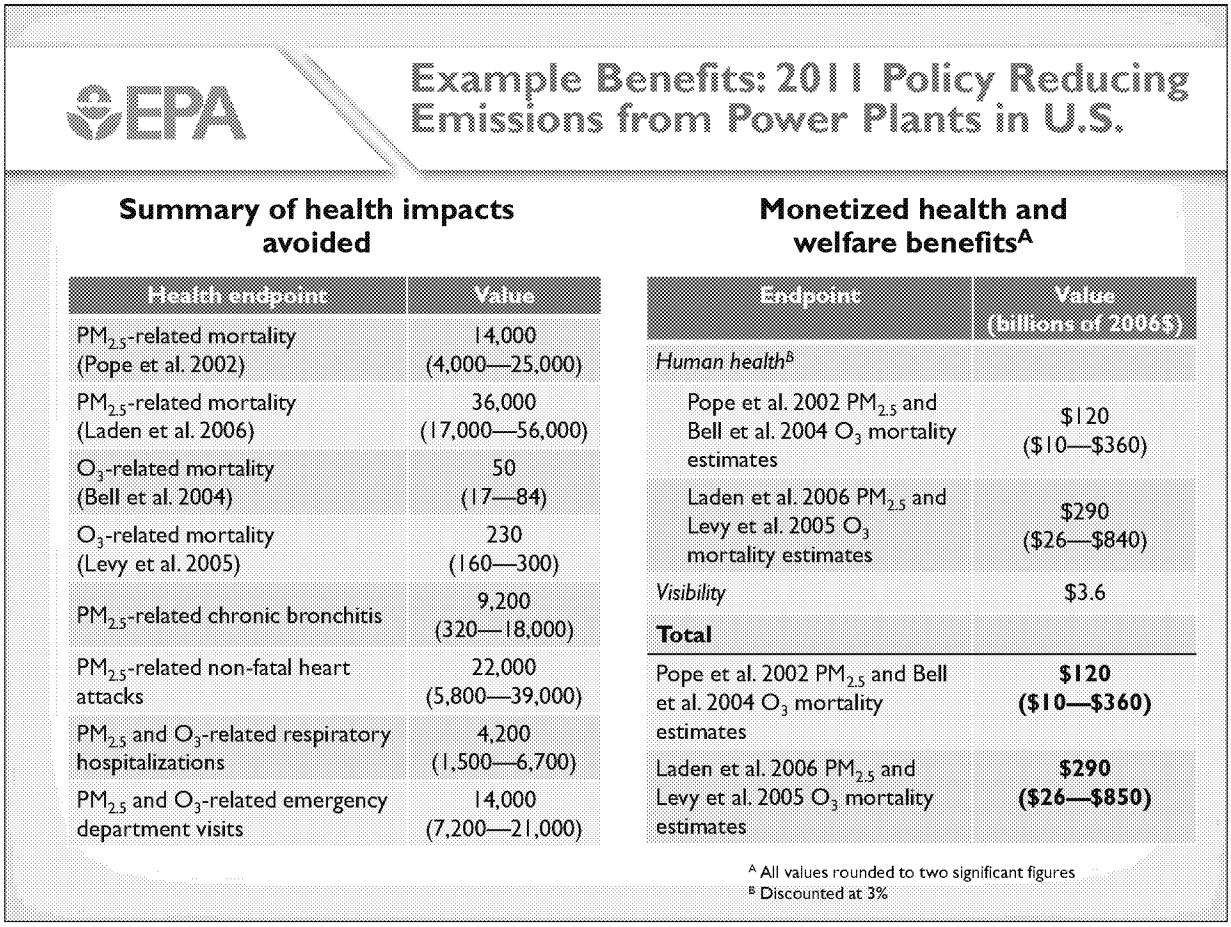
- **U.S. EPA's Environmental Benefits Mapping and Analysis Program – Community Edition (BenMAP – CE)**
  - **Free and open-source program that allows users to use data supplied by EPA or their own data to estimate the health and economic benefits of various air quality scenarios**
  - **Available at: https://www.epa.gov/benmap**



Very simplistic example of the relationship between air pollution and some health outcome that is depicted in an epidemiologic study.

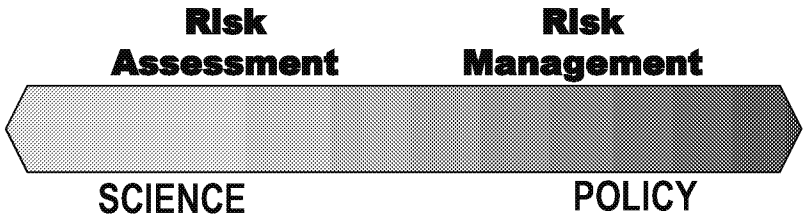
Rather simple algebraic equation is used to estimate the impact of some change in AQ.

Using the beta coefficient which is the main result from an epidemiologic study and represents the slope of the line depicted in the graph, along with other information including the baseline incidence rate for the health outcome of interest, population data that matches the epidemiologic study, and some chage in air quality it is possible to estimate the air pollutant attributable impacts.



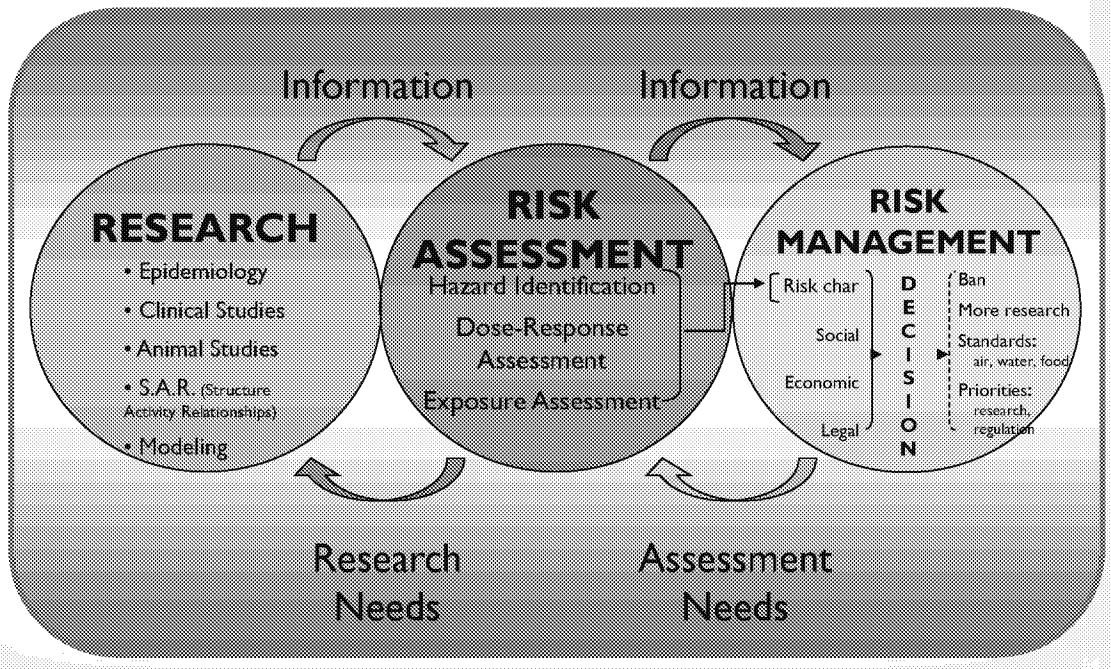
This slide highlights the fact that benefits from air pollution regulations are not small and can be rather substantial.

Risk Assessment and Risk Management are Interrelated

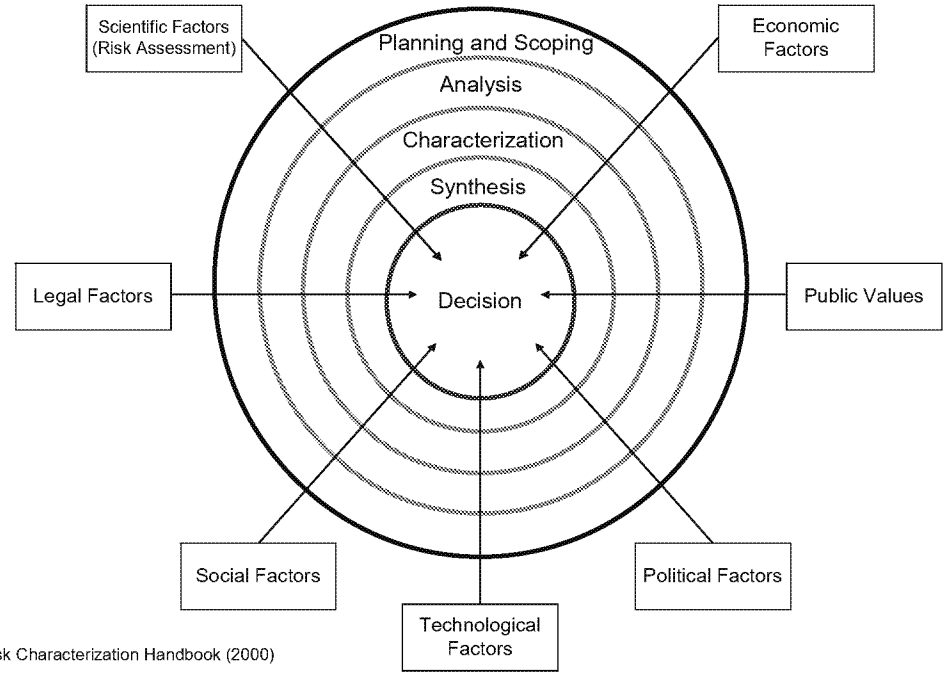


- Risk assessors and risk managers need to have a good sense of when a decision is scientific judgment versus when it is a policy decision informed by science.
- Opinions vary on how separated risk assessment and risk management should be.
- The most current frameworks recommend an iterative process.
- Transparency is key.

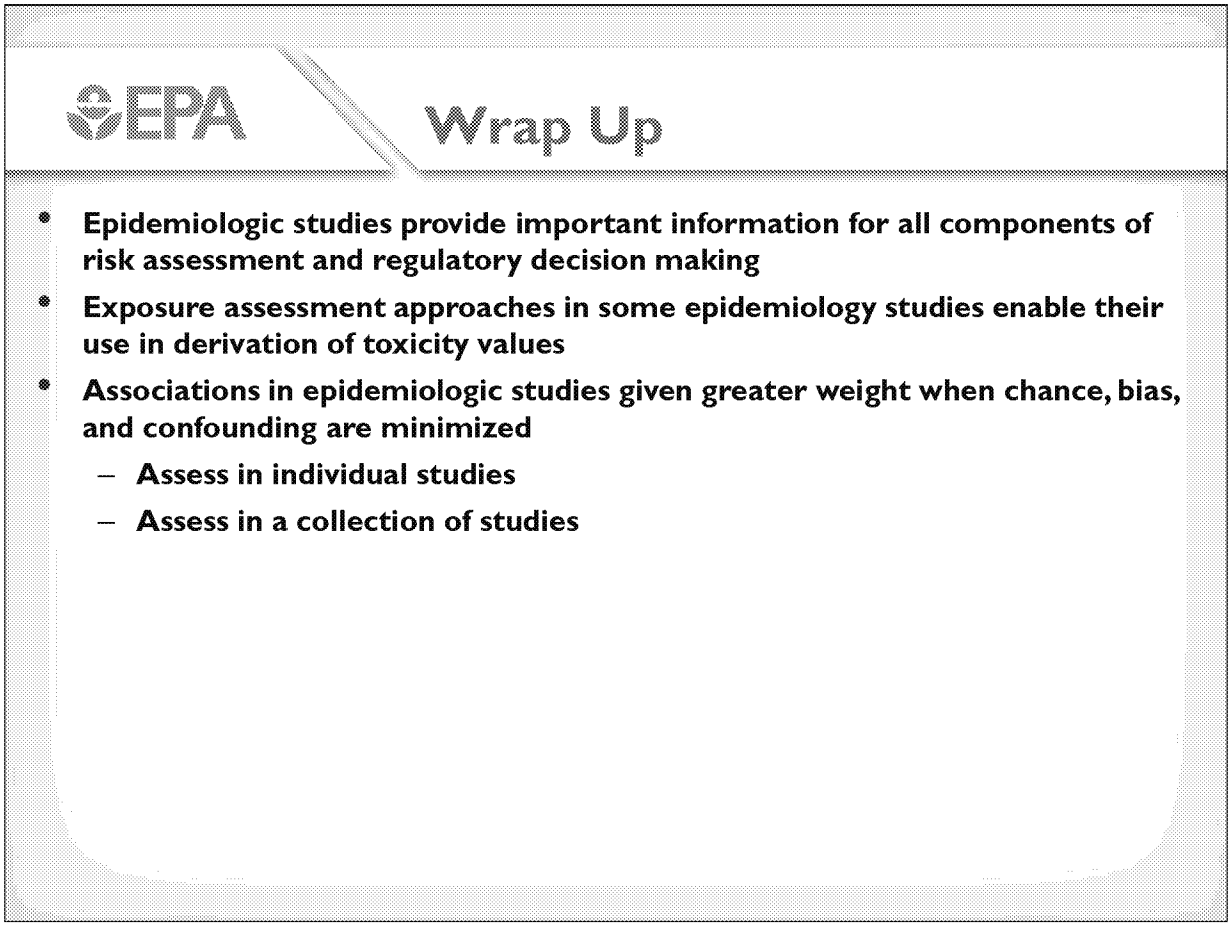
Risk Analysis Paradigm



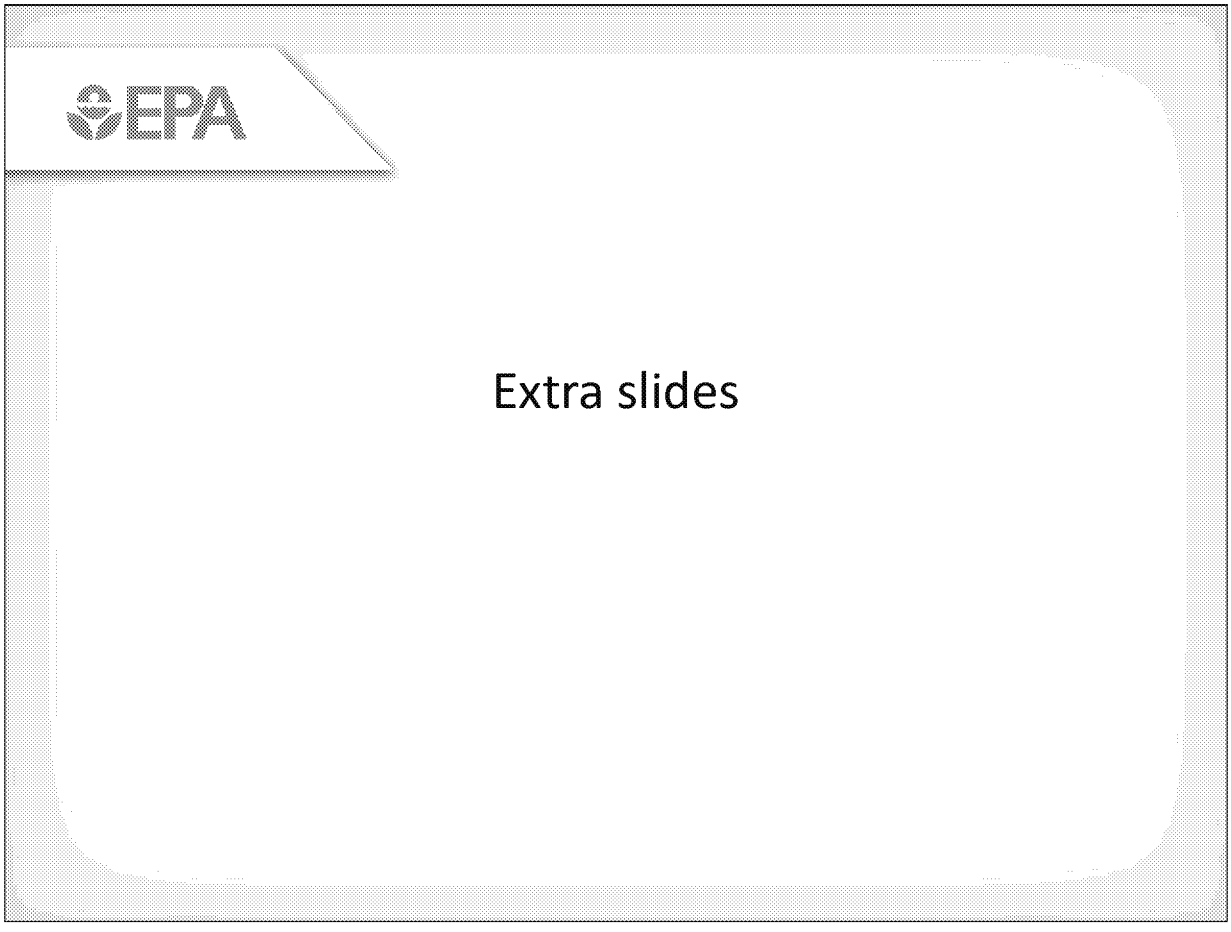
Risk Management Decision Framework



Source: EPA's Risk Characterization Handbook (2000)



EPA has been a leader in the environmental risk assessment field since it was established in 1970.
A basic paradigm (with associated terminology and concepts) guides the application of risk assessment principles, but Terms can vary by context.
Processes continue to evolve,
ORD products and guidance are crucial for EPA risk assessments.


EPA
Extra slides

Terminology

Human Health and Ecological Reference Values

Recommended or legal limits to exposure (often expressed as a dose or concentration) at or below which adverse human health or ecological effects are deemed "tolerable" or are not expected to occur.

Dose

mg/kg-day

Milligram substance per kilogram body weight per day.

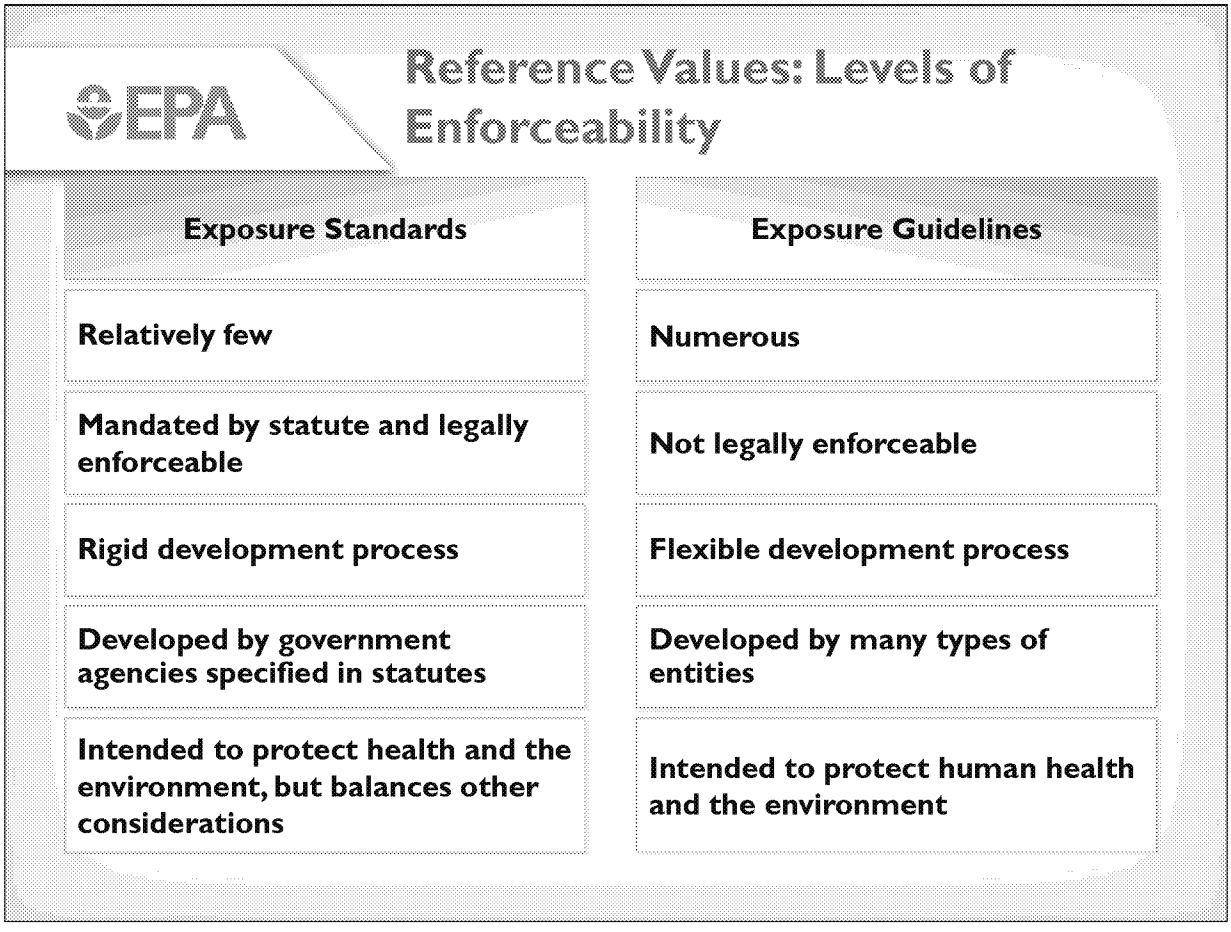
Concentration

mg/L, mg/kg, or mg/m^3

Milligram substance per liter water, kilogram soil or food, or cubic meter air.

Practical Application

Air, water, soil, and food quality standards (and other exposure limits) to protect human health and the environment.



Reference Values: Levels of Enforceability

Not all limits to chemical exposure or environmental contamination that are derived from the risk assessment process are legally enforceable. In fact, most are simply recommended limits to human exposure, with relatively few limits mandated by a regulatory statute.

Regulatory Standards, as we've discussed, are developed to set legal limits for exposures to ensure "safe" levels for the general public or a subpopulation, but they are not completely health-based. For example, when considering alternative actions for a proposed programmatic rule, agencies generally consider human health risks across the alternatives in addition to other factors (e.g., socioeconomic impacts, environmental justice, available control technologies).

There are considerably fewer regulatory standards than non-enforceable guidelines. This generally occurs because:

there is a complex legal process for the development of a standard;

standards are less adaptable to specific scenarios than guidelines, largely because many other factors must be woven into the final standard; and

a statute specifies the agency required to develop the regulations, so only the specified entities cannot develop the standard.

The takeaway message is that legally enforceable standards balance health effects with a range of other considerations to establish what is termed an "acceptable" risk level.

Guidelines are developed specifically to protect human health or the environment based solely on toxicological data. Although they are not legally enforceable, these reference values sometimes represent levels that a federal or state entity is prepared to regulate, if necessary. As a result, guidelines are often the health-based starting point for developing regulatory standards.

There are many more recommended exposure guidelines than regulatory standards. This generally occurs because:

exposure guidelines can be adapted to specific scenarios (e.g., duration, population, exposure media) to be protective of human health in these specific scenarios;

they can be developed by entities that are non-regulatory – that is, government offices not mandated to carry out a statute; state, local, and tribal governments; not-for-profit organizations); and

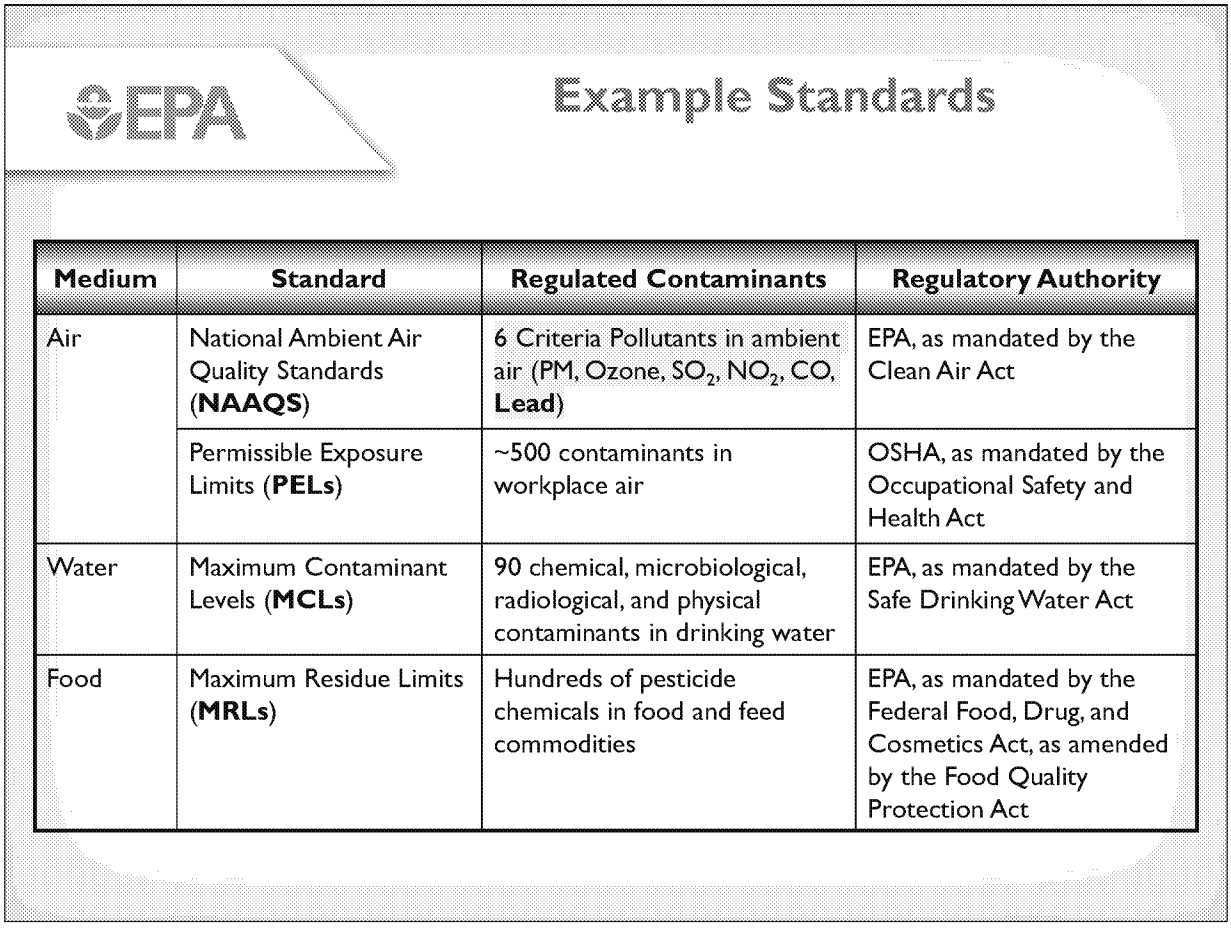
they do not need to be adapted to consider economic, engineering, or regulatory limitations to achieve the recommended dose or exposure limit, which differs from regulatory standards.

The take-away message is that these values are health-based values that can be derived by any entity using only toxicological data as the basis for the recommended level.

- Pose this question to the participants: Now that we've gone over the criteria for what defines a standard, are there any

values that we brought up in our class discussion that you now believe not to be standards?

 On the next slide is a list of the major regulatory standards developed by the Federal Government that set legal limits to chemical exposure. Let's see how many we identified in our class discussion.



Although this table is not an exhaustive list of exposure standards developed by federal agencies, it is a large subset, demonstrating just how infrequently major exposure standards are developed.
To briefly review what is on the slide, these four standards are some of the most well-known and widely applied standards in the United States.
National Ambient Air Quality Standards, or NAAQS, have been developed for only 6 principal pollutants (called criteria pollutants) in ambient air.
Permissible Exposure Levels, or PELs, on the other hand, have been developed for over 500 contaminants in workplace air.
Maximum Contaminant Levels, or MCLs, have been developed for 90 contaminants in drinking water, but this does not apply to surface water, which we will also discuss later in this course.
Notice that no standards have been set for soil – due in part to the difficulty of establishing a standard for such a complex and variable medium.
Last on this list, Maximum Residue Limits, or MRLs, are "tolerances" set for pesticide residues in food. Over 450 pesticides have been assigned tolerances or tolerance exemptions.
Notice on this slide that most of these exposure standards have been developed by the U.S. Environmental Protection Agency, with one developed by the U.S. Department of Labor's Occupational Safety and Health Administration. As we discussed in the previous slide, only federal, state, or tribal governments can pass legally enforceable standards.

We started this course with a discussion of legally enforceable standards to establish a context for human health and ecological reference values using well-known examples. We'll now depart from the discussion of standards and focus on reference values as a whole, including

More detailed discussion on entities that derive them and why

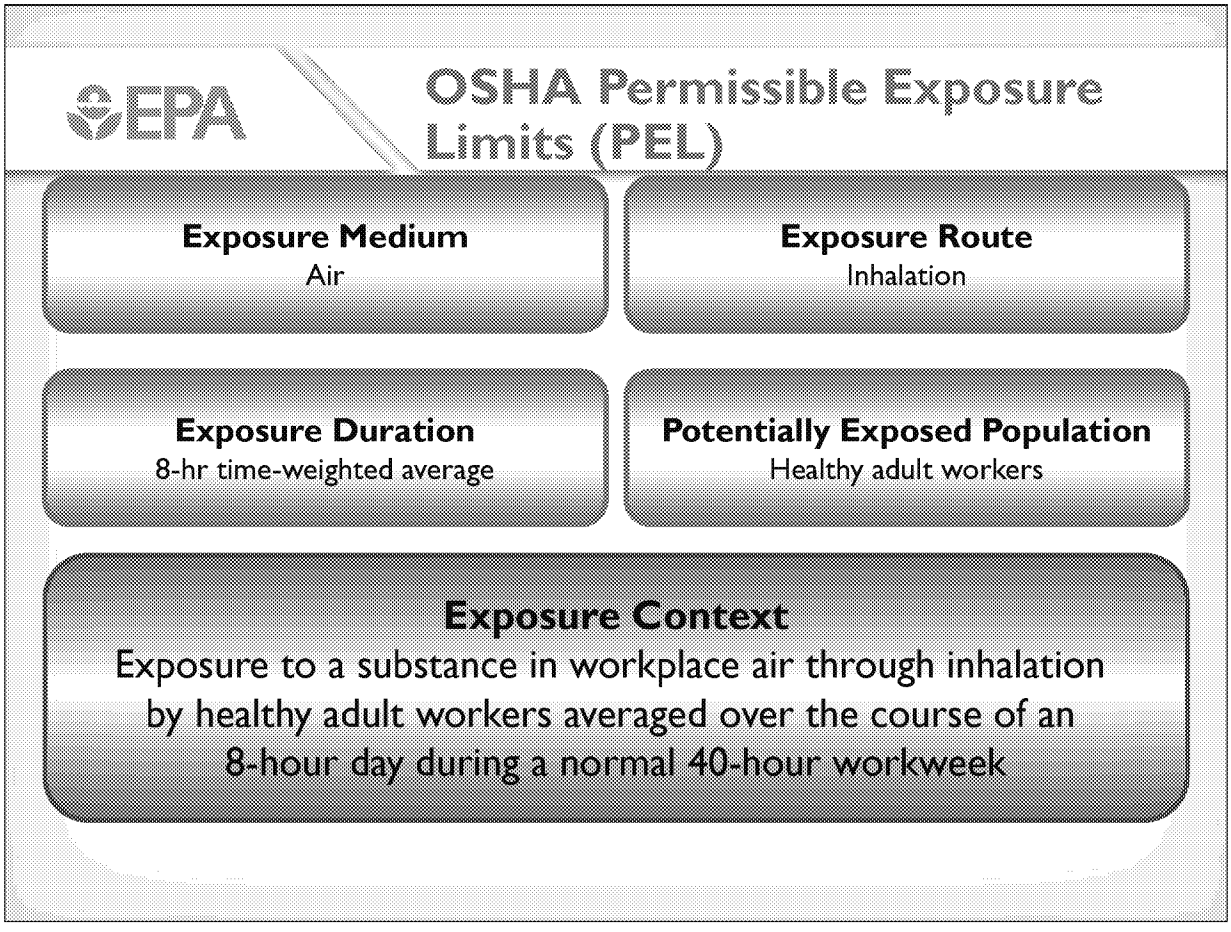
What information is needed to develop a reference value, and

How these values can be applied.

As you can see, a number of federal agencies other than EPA and OSHA, as well as state agencies, do develop reference values; however, most are recommended limits to exposure, rather than legal standards. Scientific Organizations not associated with a government agency can also develop reference values as recommended limits to exposure. For example,

The American Conference of Governmental Industrial Hygienists, or ACGIH, is a not-for-profit scientific association that develops human health reference values to enable industrial hygienists to make decisions regarding the relative safety of exposure to various chemical substances and physical agents found in the workplace.

Because so many organizations develop reference values, there is a need to centralize and prioritize these values for risk assessment and management purposes.



Exposure Context

Finally, an exposure context ties together the exposure medium, route, duration, and potentially exposed population to define the circumstances in which it is most appropriate for the reference value to be applied.
For example, OSHA PELs, which we introduced earlier as legally enforceable standards, are developed to protect workers against the health effects of exposure to hazardous substances in the workplace. So that these reference values can be used for evaluation and control purposes within this context, they were developed to incorporate the most applicable exposure specifications.
In this case, the most appropriate medium was determined to be air (although a skin designation is often provided for direct dermal contact with a chemical). The most appropriate exposure routes were therefore determined to be through inhalation of airborne particles or dermal uptake of substances on the skin. The most appropriate exposure duration was assumed to be a normal 8-hour workday in a normal 40-hour workweek, for which the exposure concentration is averaged over each 8-hour day. And because of the occupational setting, the potentially exposed population of interest is the healthy adult workers that would be present in the workplace over a 40-hr workweek.
Though we'll discuss the application of such reference values in more detail later in this course, the ability of risk assessors to tailor reference values to specific situations allows risk managers and decisionmakers to implement appropriate strategies to reduce or avoid exposures to harmful substances. In the case of PELs, these reference values are used to select appropriate control technologies and to engineer harmful substances out of a process, if possible, and if not, to provide the most appropriate level of personal protective and ventilation equipment.

Example #1: National Epidemiological and Environmental Assessment of Recreational Water (NEEAR) Study

Goal was to evaluate associations between swimming-associated illness and novel, faster indicator methods to measure water quality

- **Measured illness occurrence by questionnaire**
- **Collected and tested water samples the day of study**
- **Updated definition of GI illness (no fever required)**

NEEAR study locations

- **Located with nearby treated sewage discharges (Highest risk, best sites to develop associations with illness)**
  - **2003-2004 sites - temperate freshwater**
    - **4 beach sites on the Great Lakes**
  - **2005-2007 sites - temperate marine studies**
    - **3 beach sites: Alabama, Rhode Island, Mississippi**
- **2009 sites: "Tropical" (Puerto Rico) beach with nearby treated sewage discharges**

  "Runoff" (South Carolina) (no known sewage discharges)

2012 Recreation Water Quality Criteria (Recommendations)

Table 4. Recommended 2012 RWQC.

Criteria Elements	Estimated Illness Rate (NGI): 36 per 1,000 primary contact recreators			Estimated Illness Rate (NGI): 32 per 1,000 primary contact recreators	
	Magnitude			Magnitude	
Indicator	GM (cfu/100 mL)[a]	STV (cfu/100 mL)[a]	OR	GM (cfu/100 mL)[a]	STV (cfu/100 mL)[a]
Enterococci – marine and fresh	35	130		30	110
OR					
E. coli – fresh	126	410		100	320
Duration and Frequency: The waterbody GM should not be greater than the selected GM magnitude in any 30-day interval. There should not be greater than a ten percent excursion frequency of the selected STV magnitude in the same 30-day interval.					

[a] EPA recommends using EPA Method 1600 (U.S. EPA, 2002a) to measure culturable enterococci, or another equivalent method that measures culturable enterococci and using EPA Method 1603 (U.S. EPA, 2002b) to measure culturable *E. coli*, or any other equivalent method that measures culturable *E. coli*.

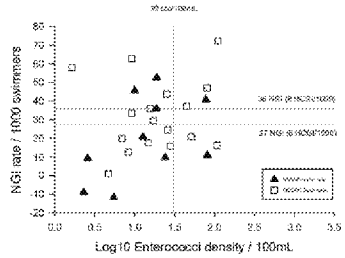


Figure 4. NEEAR marine and fresh water culture-based enterococci and illness rate data aggregated by days of similar water quality.

Approach 5

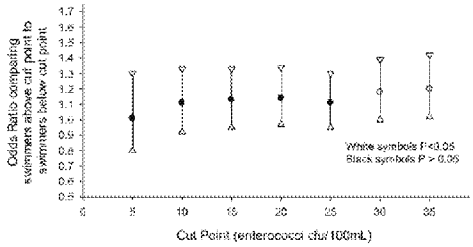
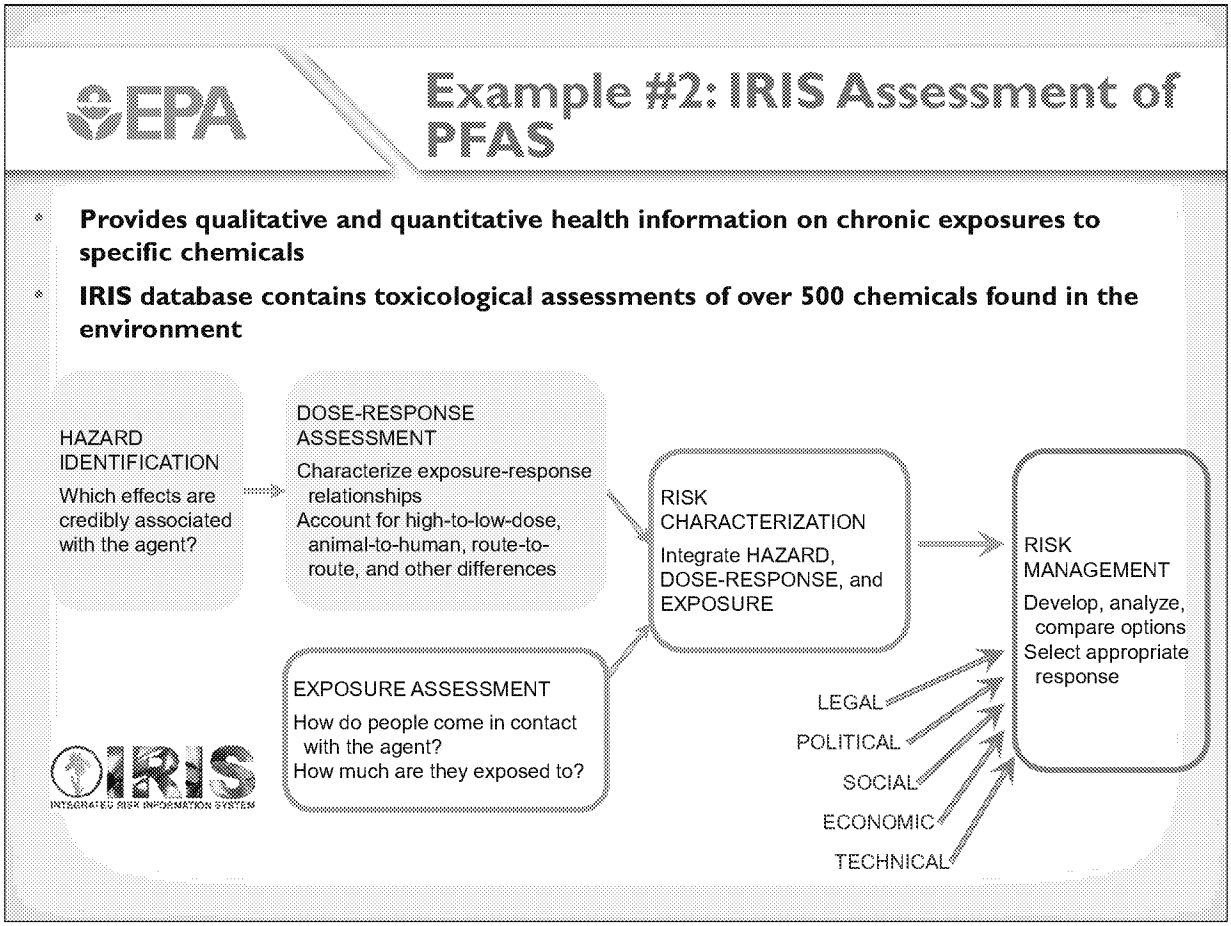


Figure 5. Adjusted odds ratios of GI illness for swimming above specific cut-points in NEEAR marine and fresh water study sites.

Based on this analysis and results illustrating the consistency between the culturable NEEAR epidemiological data to the 1986 fresh water studies, the corresponding mean estimate of illness associated with the 2012 RWQC recommendations is approximately 27 to 36 cases of NGI per 1,000 primary contact recreators for both marine and fresh water (Figures 3 and 4)

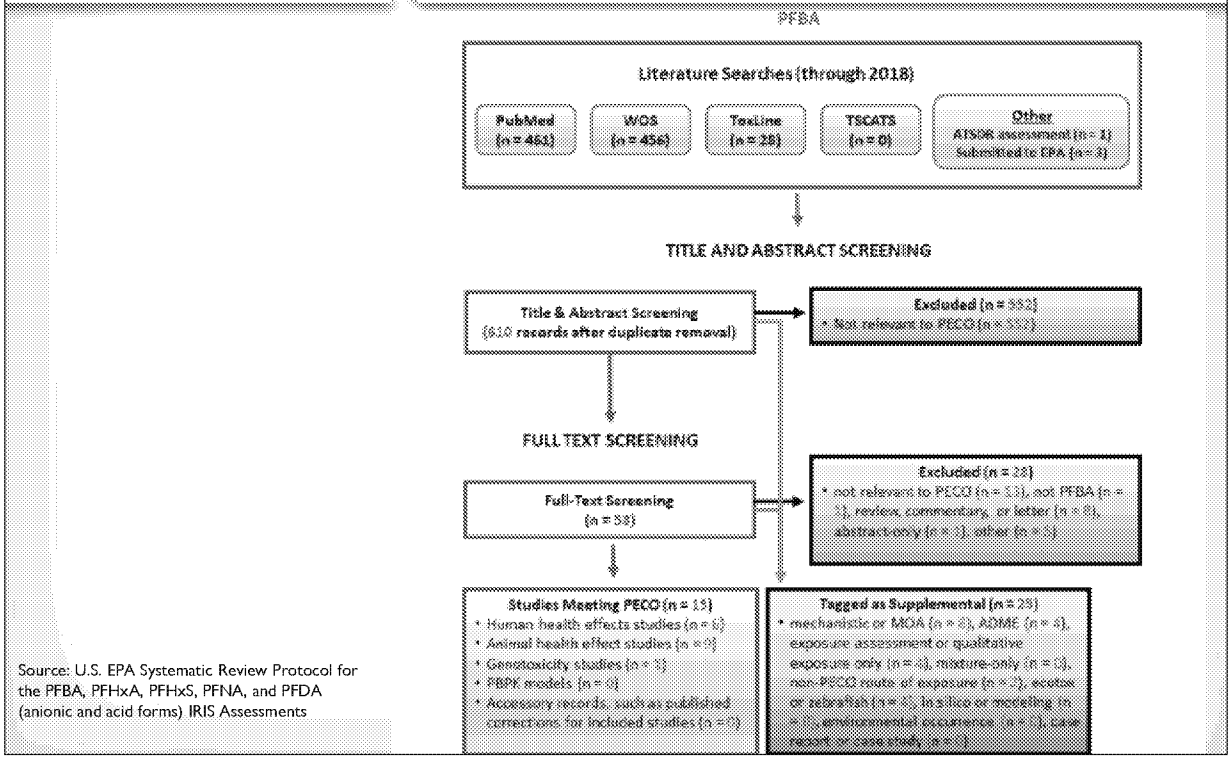
The odds ratios for swimming-associated GI illness are statistically significant (that is, $p \leq 0.05$) at enterococci densities of 30 cfu per 100 mL and 35 cfu per 100 mL. None of the other individual cut-points exhibited odds ratios that were statistically significant (lower 95% CI values are less than one in all other cases). These results indicate that the illness rates for swimming in waters with GMs in the narrow range of 30 to 35 cfu per 100 mL were significantly greater than the illness rates for swimming in waters with GMs below those levels. Similar illness rate changes are not seen outside this range. Culturable Enterococcus conclusion Taken together, the set of approaches described above provide lines of evidence to support the recommendation of a GM criterion value of 30 or 35 cfu per 100 mL. These approaches also provide evidence that the recommended RWQC are similarly protective of the designated use of primary contact recreation in both marine and fresh water. EPA is presenting two sets of criteria (consisting of a GM and related STV) associated with two different illness rates. EPA recommends that states make a risk management decision to choose one or the other set.

NEEAR study was primary study in which set wq criteria recommendations– however several other epidemiological studies were considered in the determination.



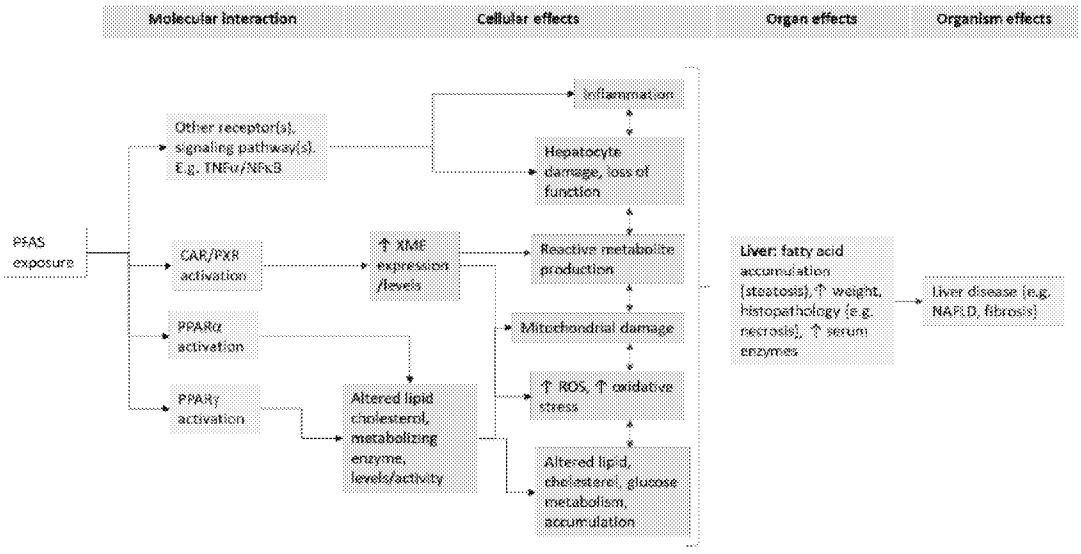
The Integrated Risk Information System, or IRIS, is a human health assessment program that evaluates hazards that may result from lifetime exposure to environmental contaminants. IRIS toxicological assessments use health evidence both quantitatively and qualitatively to evaluate chronic exposures to more than 500 different chemicals found in the environment. You may have noticed that I said "toxicological" assessments. Often, the bulk of health evidence for IRIS chemicals comes from toxicological studies, though evidence from epidemiologic studies is integrated into IRIS assessments when available. **CHANGE TO PFAS EXAMPLE

IRIS PFAS Systematic Literature Search



Source: U.S. EPA Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments

Preliminary mechanistic pathway for PFAS



Source: U.S. EPA Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments

Assessing Bradford Hill Guidelines

- **Considerations for epidemiology data**
  - **Temporal relationship (exposure precedes disease)**
  - **Consistency across studies**
  - **Strength of association (considering units of exposure)**
  - **Exposure-response relationship**
- **Considerations drawing in other data**
  - **Plausibility and coherence**
- **Considerations of low utility**
  - **Specificity (single cause, single effect)**

Evaluating Individual Studies: Inadequate Exposure-Response Data

- **Many epidemiology studies provide little or no information about exposure-response relation**
  - **"Ever-never" exposures; limited range of exposures**
  - **Duration may be a weak proxy for total exposure if exposure changes (decreases) over time**
- **Absence of exposure-response analysis does not invalidate the study, and does not negate its usefulness in the hazard identification phase of risk assessment**

Evaluating Exposure-Response Data from Individual Studies

- **Effect of non-differential exposure misclassification on exposure-response curve**
- **Non-linear patterns of increasing exposure-response often seen**

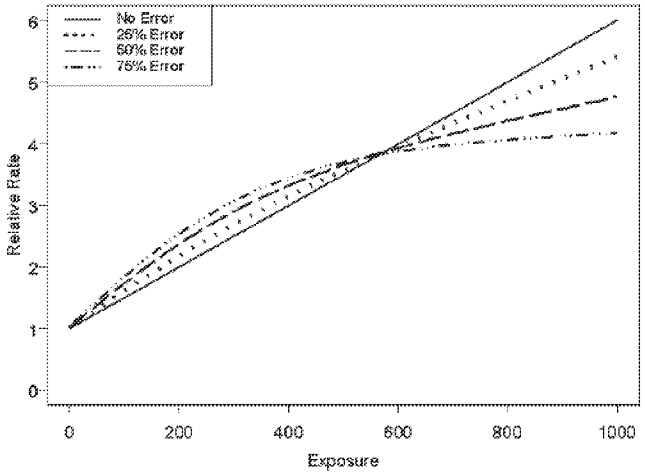


Figure 3. Results from a simulation study of the effect of random misclassification of exposures on a true linear exposure relationship.

Attenuation of exposure-response curves in occupational cohort studies at high exposure levels.
Stayner L. et al. *Scand J Work Environment Health*. 2003; 29: 317-324.

HSR 101

Quantitative Synthesis Procedures?

Types of procedures

- Meta-analysis
- Pooled analysis
- Meta-regression

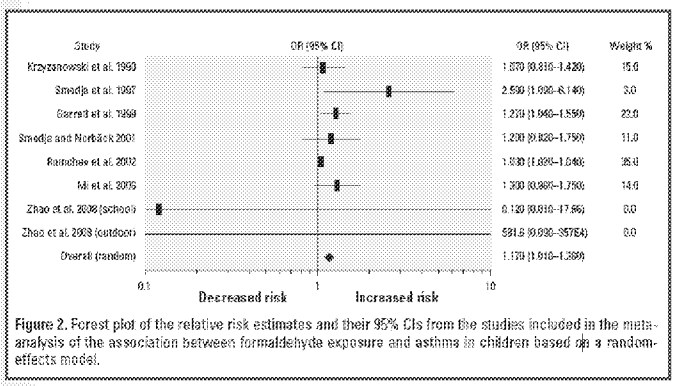


Figure 2. Forest plot of the relative risk estimates and their 95% CIs from the studies included in the meta-analysis of the association between formaldehyde exposure and asthma in children based on a random-effects model.

Source: McGwin et al. (2010) Environ Health Perspect 118:313-317.

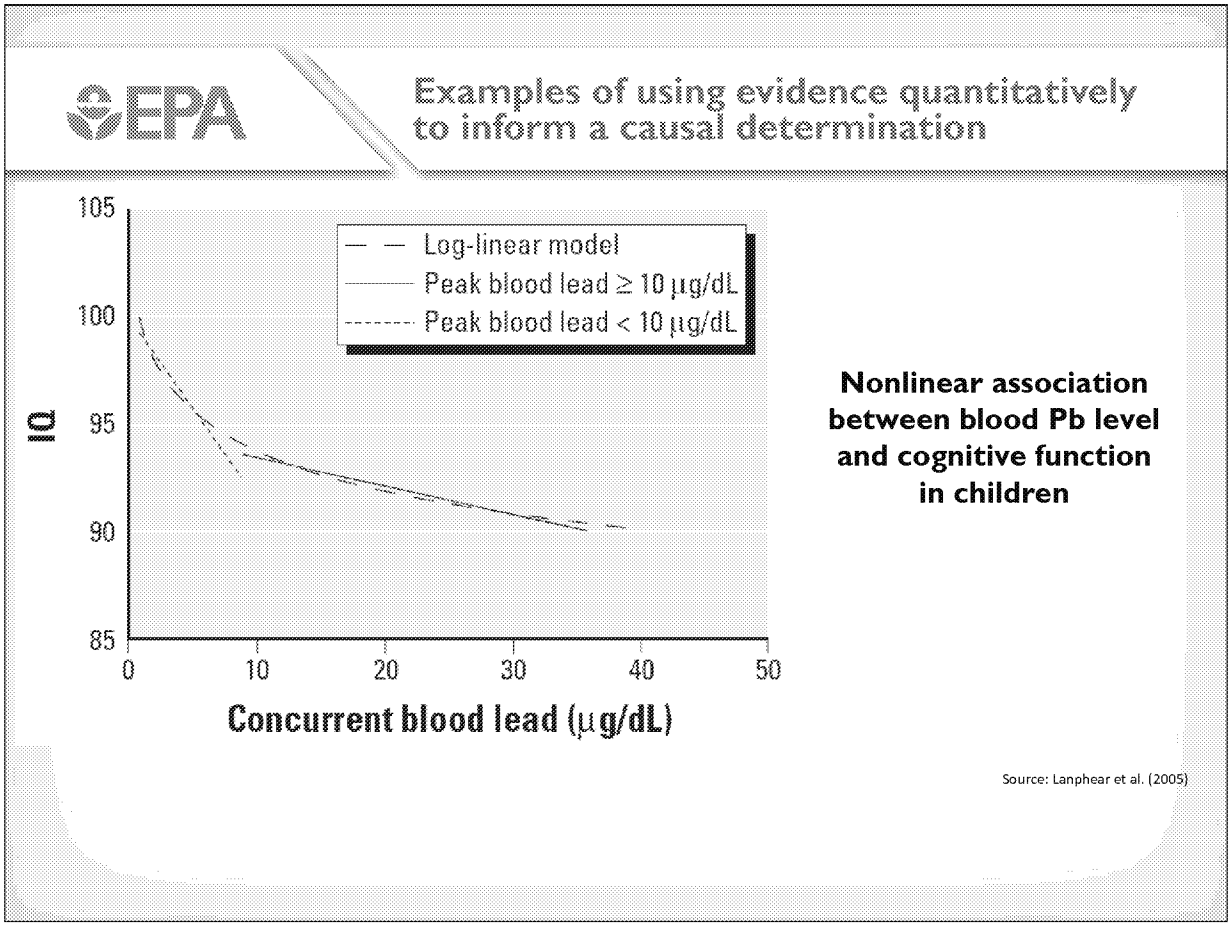
Advantages

- Can gain precision
- Can evaluate effects of different aspects of study design

Disadvantages

- Feasibility
- Exclusions (based on type, access to data) may affect results
- Marginal cost may be high, marginal gain may be low

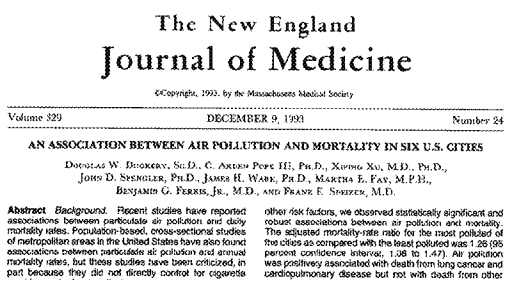
Meta-analysis: A general term to denote the collection of statistical methods and techniques used to aggregate/synthesize and compare the results from several related studies in a systematic manner.
Meta-regression: Regress the observed effect sizes on one or multiple study characteristics.



Here we can see how the results of epidemiologic studies can be used quantitatively, in this case to characterize the non-linear concentration-response function for blood lead level and cognitive function in children. We can see that the steepest declines in IQ occur at the lowest blood Pb concentrations (<10 ug/dl) and that the slope is less steep when blood lead levels are >10 ug/dl.

Example: Air pollution and mortality

- **Environmental epidemiology example**
  - **Association between environmental exposure (air pollution) and a health outcome (mortality) in the US**
- **Prospective cohort**
  - **8,111 adults in 6 US cities**
  - **Followed for 14-16 years or until death**
  - **Time-series data structure**



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AN ASSOCIATION BETWEEN AIR POLLUTION AND MORTALITY IN SIX U.S. CITIES

DOUGLAS W. DOCKERY, SC.D., C. ARDEN POPE III, PH.D., XIPING XU, M.D., PH.D., JOHN D. SPENGLER, PH.D., JAMES H. WARE, PH.D., MARTHA E. FAY, M.P.H., BENJAMIN G. FERRIS, JR., M.D., AND FRANK E. SPEIZER, M.D.

Abstract *Background.* Recent studies have reported associations between particulate air pollution and daily mortality rates. Population-based, cross-sectional studies of metropolitan areas in the United States have also found associations between particulate air pollution and annual mortality rates, but these studies have been criticized, in part because they did not directly control for cigarette

other risk factors, we observed statistically significant and robust associations between air pollution and mortality. The adjusted mortality-rate ratio for the most polluted of the cities as compared with the least polluted was 1.26 (95 percent confidence interval, 1.08 to 1.47). Air pollution was positively associated with death from lung cancer and cardiopulmonary disease but not with death from other

Example: Air pollution and mortality

- **Results**

Table 2. Adjusted Mortality-Rate Ratios Estimated from Cox Proportional-Hazards Models.*

Variable	All Subjects	Men	Women
		rate ratio (95% CI)	
Current smoker	1.59 (1.31–1.92)	1.75 (1.32–2.32)	1.54 (1.16–2.04)
25 Pack-years of smoking	1.26 (1.16–1.38)	1.25 (1.12–1.39)	1.18 (1.00–1.41)
Former smoker	1.20 (1.01–1.43)	1.17 (0.93–1.48)	1.34 (1.02–1.77)
10 Pack-years of smoking	1.15 (1.08–1.23)	1.16 (1.09–1.25)	1.15 (0.97–1.36)
Less than high-school education	1.19 (1.06–1.33)	1.22 (1.06–1.41)	1.13 (0.95–1.35)
Body-mass index	1.08 (1.02–1.14)	1.03 (0.95–1.12)	1.11 (1.03–1.20)
City			
Portage, Wis.†	1.00 (----)	1.00 (----)	1.00 (----)
Topeka, Kans.	1.01 (0.82–1.24)	1.04 (0.79–1.36)	0.97 (0.71–1.34)
Harriman, Tenn.	1.17 (0.97–1.41)	1.21 (0.96–1.54)	1.07 (0.79–1.45)
Watertown, Mass.	1.07 (0.89–1.28)	0.94 (0.75–1.20)	1.22 (0.93–1.61)
St. Louis	1.14 (0.96–1.36)	1.15 (0.91–1.44)	1.13 (0.86–1.50)
Steubenville, Ohio	1.26 (1.06–1.50)	1.29 (1.03–1.62)	1.23 (0.93–1.61)

*Rates have been adjusted for age, sex, and all other variables listed in the table. The rate ratios for body-mass index are for an increase of 4.52 (1 SD). CI denotes confidence interval.
†City-specific rate ratios are all expressed in relation to Portage.

Table 4. Estimated Mortality-Rate Ratios for the Most Polluted City as Compared with the Least Polluted City, with Fine Particles Used as the Indicator of Air Pollution, in Selected Models.*

Model No.	Variables Included†	Rate Ratio (95% CI)‡
1	Fine particles	1.31 (1.13–1.52)
2	Model 1 + all smoking variables	1.29 (1.11–1.49)
3	Model 2 + high-school education	1.26 (1.08–1.47)
4	Model 3 + body-mass index	1.26 (1.08–1.47)
5	Model 4 + occupational exposure	1.26 (1.08–1.46)
6	Model 5, excluding 1439 subjects with hypertension	1.25 (1.04–1.50)
7	Model 5, excluding 561 subjects with diabetes	1.29 (1.09–1.52)

*The city with the highest level of fine-particulate air pollution was Steubenville, Ohio, and that with the lowest was Portage, Wisconsin. In addition to the variables specified, rates have been adjusted for age and sex.
†Subjects with hypertension were those who had been treated for high blood pressure within 10 years before enrollment; subjects with diabetes were those who had ever been told by a doctor that they had diabetes, had glucose in their urine, or had too much glucose in their blood.
‡CI denotes confidence interval.

- Really an important study that has greatly contributed to current air quality standards in the US
  - Not the only one!

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP3860.

Cardiopulmonary Effects of Fine Particulate Matter Exposure among Older Adults, during Wildfire and Non-Wildfire Periods, in the United States 2008–2010

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Background: The effects of exposure to fine particulate matter ($PM_{2.5}$) during wildland fires are not well understood in comparison with $PM_{2.5}$ exposures from other sources.

Objectives: We examined the cardiopulmonary effects of short-term exposure to $PM_{2.5}$ on smoke days in the United States to evaluate whether health effects are consistent with those during non-smoke days.

Methods: We examined cardiopulmonary hospitalizations among adults ≥65 y of age, in U.S. counties ($n=692$) within 200 km of 123 large wildfires during 2008–2010. We evaluated associations during smoke and non-smoke days and examined variability with respect to modeled and observed exposure metrics. Poisson regression was used to estimate county-specific effects at lag days 0–6 (L0–6), adjusted for day of week, temperature, humidity, and seasonal trend. We used meta-analyses to combine county-specific effects and estimate overall percentage differences in hospitalizations expressed per 10-$\mu g/m^3$ increase in $PM_{2.5}$.

Results: Exposure to $PM_{2.5}$ on all days and locations was associated with increased hospitalizations on smoke and non-smoke days using modeled

Example- Wildfires and Hospitalizations

- **Hospitalizations among Medicare population 65+,**
  - Respiratory: 1,032,268
  - Asthma, Bronchitis, or Wheezing: 82,463
  - Cardiovascular: 2,558,602
- **Estimated exposure to wildfire smoke**
- **Estimated excess risk of cardiovascular, asthma/bronchitis/wheezing, and respiratory hospitalizations**
- **Results**
  - **Respiratory hospitalizations: 1.08% (0.28, 1.89) increase on days exposed to smoke**
  - **Asthma/bronchitis/wheezing hospitalizations 6.90% (3.71, 10.11) increase on days exposed to smoke**
  - **Cardiovascular hospitalizations: 0.61% (0.09, 1.14) increase on days exposed to smoke**

Overview of Integrated Risk Information System (IRIS) study evaluation process.

Study evaluation process

- Develop assessment-specific considerations
- Pilot testing (and possible refinement)
- Independent evaluation by two reviewers
- Conflict resolution
- Finalize domain judgments and overall study rating

(b) Individual evaluation domains

Animal	Epidemiology
Selection and performance • Allocation • Observational bias/confounding	Participant selection
Confounding/variable control	Confounding
Selective reporting and attrition	Selective reporting
Exposure methods sensitivity • Chemical administration and characterization • Exposure timing, frequency, and duration	Exposure measurement
Outcome measures and results display • Endpoint sensitivity and specificity • Results presentation	Outcome ascertainment Analysis
Reporting quality	Other sensitivity

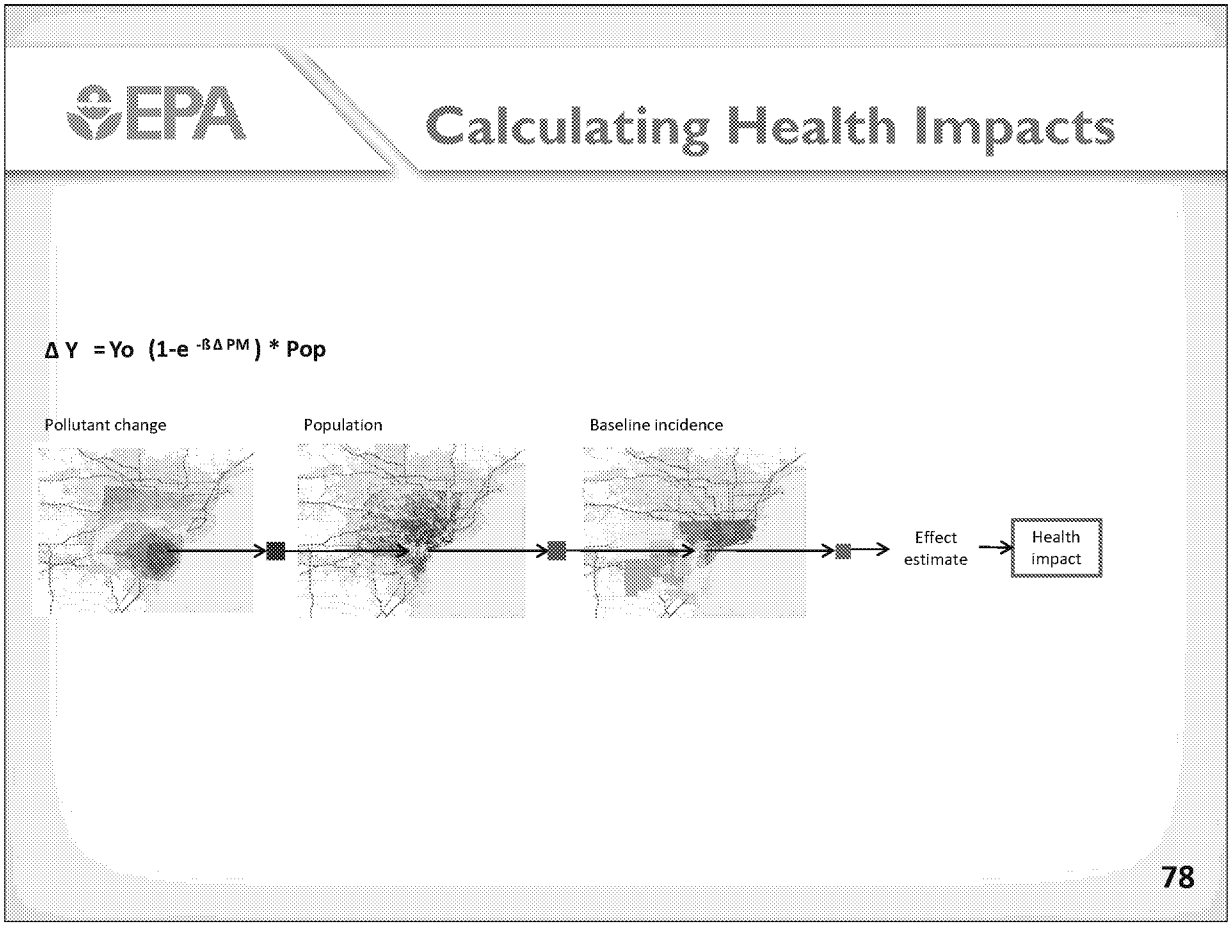
Domain judgments

Judgment	Interpretation
Good	Appropriate study conduct relating to the domain and minor deficiencies not expected to influence results.
Adequate	A study that may have some limitations relating to the domain, but they are not likely to be severe or to have a notable impact on results.
Deficient	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.
Critically Deficient	A serious flaw identified that makes the observed effect(s) uninterpretable. Studies with a critical deficiency will almost always be considered 'uninformative' overall.

Overall study rating for an outcome

Rating	Interpretation
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal; sensitive methodology.
Medium	Possible deficiencies or concerns noted, but resulting bias or lack of sensitivity is unlikely to be of a notable degree.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results unusable for hazard identification or dose response.

Source: U.S. EPA Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA (anionic and acid forms) IRIS Assessments



In the previous slide we defined the general health impact function, but how do you then take that and calculate the health impacts? The first step is identifying some spatial domain over which you want to estimate the health impacts.

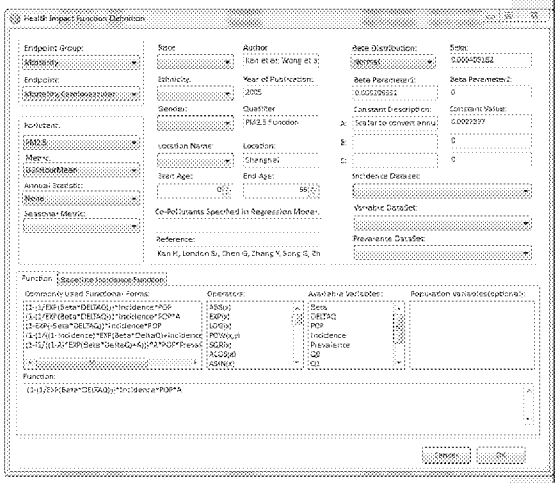
Using either modeled or monitored air quality data you would identify the pollutant change of interest.
For that same spatial domain, obtain population data as well as baseline incidence data for the health effect being examined.
Lastly, the effect estimate from the epidemiology study is used to calculate the health impact.

To ensure the proper calculation of the health impact the population and baseline incidence data needs to match the characteristics of the study that the effect estimate is derived from. For example, if the epidemiology study only consists of people over the age of 25 and focuses on mortality then the population and baseline incidence data should match.

Health Impact Functions

- **BenMAP-CE contains over a 100 health impact functions for the U.S. and China**
- **Users can download EPA's default functions for $PM_{2.5}$**
  - **EPA's previous functions for NO_2, SO_2, and lead are also available**
- **Users can add and edit their own health impact functions using the function editor**

$$\Delta Y = Y_o (1 - e^{-\beta \Delta PM}) * Pop$$



BenMAP-CE's Health Impact Function Editor

Avg time (8 hr max, 1 hour max, 2 hour max). Ensuring we have the proper pop and incidence data.